DRAFT FOR PUBLIC COMMENT

Air Toxics Hot Spots Program Risk Assessment Guidelines:

Technical Support Document for Determining Cancer Potency Factors

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Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

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Preface

The Risk Assessment Advisory Commission (RAAC) report made several recommendations regarding harmonization within Cal/EPA and with US EPA. The Technical Support Document for Determining Cancer Potency Factors (TSD) has made an effort to implement the RAAC recommendations regarding harmonization both in spirit and in substance. For example, the cancer unit risk and potency factor values developed by OEHHA that are contained in the TSD were reviewed by a Cal/EPA working group to ensure agency-wide consistency and harmonization.

Currently, OEHHA uses a toxic equivalency factor procedure for polychlorinated dibenzo-*p*-dioxins and dibenzofurans that differs slightly from the procedures used by US EPA. This document proposes adoption of US EPA's International Toxicity Equivalency Factors (ITEFs) for determining cancer unit risk and potency values for these chemicals; this is discussed in Appendix A. The document proposes to adopt 12 US EPA Integrated Risk Information System (IRIS) cancer unit risk values, in lieu of developing or using other Cal/EPA values. This is summarized in the Unit Risk and Cancer Potency Table on pages 2-5. In addition, the TSD has identified and evaluated 29 other chemicals for which Cal/EPA cancer unit risk values differ from corresponding US EPA IRIS values; this is discussed on page 18 and in Appendices E and F. Fifteen of these 29 chemicals were developed under the Toxic Air Contaminant (TAC) program; the other 14 were developed under the Proposition 65 program. All 29 of the Cal/EPA values received external peer review and public comments prior to adoption by the program of origin. Revising these numbers requires the original program to reconsider the value in an open public process. For example, the Air Resources Board and Scientific Review Panel has established a specific petition process to reconsider values adopted under the TAC program. We would appreciate your comments on how the harmonization process could proceed further, particularly for those chemicals for which the Cal/EPA and US EPA unit risk values are essentially similar (for example, less than a two-fold difference).

As indicated above, the document proposes for adoption 12 US EPA IRIS cancer unit risk values. Currently, US EPA is considering revisions to its cancer risk assessment guidelines. Some of the proposed changes may modify the cancer unit risk values only slightly. We would appreciate your comments on whether we should automatically update these twelve specific US EPA cancer unit risk values if they are revised. For example, we anticipate that some changes in potency slopes and unit risk values will result from changing the body weight scaling factor from 2/3 to 3/4 power.

We believe the RAAC report has provided useful insight to the Cal/EPA risk assessment processes. Our intent has been to move forward to consider RAAC recommendations and to incorporate them into existing processes and programs on an ongoing basis.

Please direct any inquiries concerning the workshops to Dr. John Budroe of the Air Toxicology and Epidemiology Section at (510) 540-3055. Please direct your written comments regarding the document to Ms. Sharon Davis, Office of Environmental Health Hazard Assessment, 601 North 7th Street, MS-241, P.O. Box 942732, Sacramento CA 94234-7320.

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INTRODUCTION

The Technical Support Document (TSD) for Determining Cancer Potency Factors provides technical information support for the Air Toxics Hot Spots Program Risk Assessment Guidelines: Part II. Evaluation of Health Effects of Carcinogens. The TSD consists of 9 sections:

1. The TSD introduction.

2. A lookup table containing unit risk and cancer potency values.

3. A description of the methodologies used to derive the unit risk and cancer potency values listed in the lookup table.

4. Chemical-specific summaries of the information used to derive unit risk and cancer potency values.

5. A description of the use of toxicity equivalency factors for determining unit risk and cancer potency factors for polychlorinated dibenzo-*p*-dioxins and dibenzofurans (Appendix A).

6. A listing of Toxic Air Contaminant documents approved by the California Air Resources Board (Appendix B).

7. Descriptions of the International Agency for Research on Cancer (IARC) and U.S. Environmental Protection Agency (US EPA) carcinogen classifications (Appendix C).

8. An asbestos quantity conversion factor for calculating asbestos concentrations expressed as 100 fibers/m^3 from asbestos concentrations expressed as µg/m^3 (Appendix D).

9. US EPA IRIS inhalation unit risk and oral cancer potency factors available for chemicals listed in the TSD (Appendix E).

10. A listing of Hot Spots cancer unit risk values which differ from corresponding US EPA IRIS inhalation unit risk factors. (Appendix F).

Hot Spots Unit Risk and Cancer Potency Values

Chemical		Chemical Abstract Service (CAS) Number	Source	Unit Risk $(\mu g/m^3)^{-1}$	Slope Factor $(mg/kg\text{-}day)^{-1}$	US EPA Class[C]	IARC Class[C]
Acetaldehyde		75-07-0	TAC	2.7 E-6	1.0 E-2	B2	2B
Acetamide		60-35-5	RCHAS-E	2.0 E-5	7.0 E-2	NC	2B
Acrylamide		79-06-1	IRIS	1.3 E-3	4.5 E+0	B2	2A
Acrylonitrile		107-13-1	RCHAS-S	2.9 E-4	1 .0 E+0	B1	2A
Allyl chloride		107-05-1	RCHAS-S	6.0 E-6	2.1 E-2	C	3
2-Aminoanthraquinone		117-79-3	RCHAS-E	9.4 E-6	3.3 E-2	NC	3
Aniline		62-53-3	IRIS	1.6 E-6	5.7 E-3	B2	3
Arsenic (inorganic)	(inhalation)	7440-38-2	TAC	3.3 E-3	1.2 E+1	A	1
	(oral)		IRIS		1.5 E+0		
Asbestos		1332-21-4	TAC	6.3 E-2	NA	A	1
				1.9 E-4[#]			
Benz[*a*]anthracene[BaP]	(inhalation)	56-55-3	TAC	1.1 E-4	3.9 E-1	B2	2A
	(oral)				1.2 E+0		
Benzene		71-43-2	TAC	2.9 E-5	1.0 E-1	A	1
Benzidine		92-87-5	RCHAS-S	1.4 E-1	5.0 E+2	A	1
Benzo[*a*]pyrene	(inhalation)	50-32-8	TAC	1.1 E-3	3.9 E+0	B2	2A
	(oral)				1.2 E+1		
Benzo[*b*]fluoranthrene[BaP]	(inhalation)	205-99-2	TAC	1.1 E-4	3.9 E-1	B2	2B
	(oral)				1.2 E+0		
Benzo[*j*]fluoranthrene[BaP]	(inhalation)	205-82-3	TAC	1.1 E-4	3.9 E-1	NC	2B
	(oral)				1.2 E+0		
Benzo[*k*]fluoranthrene[BaP]	(inhalation)	207-08-9	TAC	1.1 E-4	3.9 E-1	B2	2B
	(oral)				1.2 E+0		
Benzyl chloride		100-44-7	IRIS	4.9 E-5	1.7 E-1	B2	2B
Beryllium		7440-41-7	IRIS	2.4 E-3	4.3 E+0	B2	1
Bis(2-chloroethyl) ether		111-44-4	RCHAS-S	7.1 E-4	2.5 E+0	B2	3
Bis(chloromethyl)ether		542-88-1	RCHAS-S	1.3 E-2	4.6 E+2	A	1
1,3-Butadiene		106-99-0	TAC	1.7 E-4	3.4 E+0	B2	2A
Cadmium (and compounds)		7440-43-9	TAC	4.2 E-3	1.5 E+1	B1	1
Carbon tetrachloride		56-23-5	TAC	4.2 E-5	1.5 E-1	B2	2B
Chlorinated dibenzo-*p*-dioxins[A]		1746-01-6	TAC			B2	2B
2,3,7,8-Tetrachlorodibenzo-*p*-dioxin				3.8 E+1	1.3 E+5		
1,2,3,7,8-Pentachlorodibenzo-*p*-dioxin				1.9 E+1	6.5 E+4		
1,2,3,4,7,8-Hexachlorodibenzo-*p*-dioxin				3.8 E+0	1.3 E+4		
1,2,3,6,7,8-Hexachlorodibenzo-*p*-dioxin				3.8 E+0	1.3 E+4		
1,2,3,7,8,9-Hexachlorodibenzo-*p*-dioxin				3.8 E+0	1.3 E+4		
1,2,3,4,6,7,8-Heptachlorodibenzo-*p*-dioxin				3.8 E-1	1.3 E+3		
1,2,3,4,5,6,7,8-Octachlorodibenzo-*p*-dioxin				3.8 E-2	1.3 E+2		

Footnotes

A	see Appendix A
BaP	see benzo[*a*]pyrene TAC document
C	see Appendix C
L	pending Air Resources Board approval
NA	not available
NC	not classified
#	[100 PCM fibers/m^3]$^{-1}$; see Appendix D
*	can be calculated using PEF factors contained in the benzo[a]pyrene TAC document

Source Key

TAC	Toxic Air Contaminant document, Office of Environmental Health Hazard Assessment (OEHHA)
RCHAS-S	Standard Proposition 65 document, OEHHA
IRIS	Integrated Risk Information System, U.S. Environmental Protection Agency (US EPA)
RCHAS-E	Expedited Proposition 65 document, OEHHA
ATES	Air Toxicology and Epidemiology Section document, OEHHA
PETS	Pesticide and Environmental Toxicology Section document, OEHHA

Hot Spots Unit Risk and Cancer Potency Values

Chemical		Chemical Abstract Service (CAS) Number	Source	Unit Risk $(\mu g/m^3)^{-1}$	Slope Factor $(mg/kg\text{-}day)^{-1}$	US EPA Class[C]	IARC Class[C]
Chlorinated dibenzofurans[A]		5120-73-19	TAC			B2	NC
2,3,7,8-Tetrachlorodibenzofuran				3.8 E+0	1.3 E+4		
1,2,3,7,8-Pentachlorodibenzofuran				1.9 E+0	6.5 E+3		
2,3,4,7,8-Pentachlorodibenzofuran				1.9 E+1	6.5 E+4		
1,2,3,4,7,8-Hexachlorodibenzofuran				3.8 E+0	1.3 E+4		
1,2,3,6,7,8-Hexachlorodibenzofuran				3.8 E+0	1.3 E+4		
1,2,3,7,8,9-Hexachlorodibenzofuran				3.8 E+0	1.3 E+4		
2,3,4,6,7,8-Hexachlorodibenzofuran				3.8 E+0	1.3 E+4		
1,2,3,4,6,7,8-Heptachlorodibenzofuran				3.8 E-1	1.3 E+3		
1,2,3,4,7,8,9-Heptachlorodibenzofuran				3.8 E-1	1.3 E+3		
1,2,3,4,5,6,7,8-Octachlorodibenzofuran				3.8 E-2	1.3 E+2		
Chlorinated paraffins		108171-26-2	RCHAS-E	2.5 E-5	8.9 E-2	NC	2B
Chloroform		67-66-3	TAC	5.3 E-6	1.9 E-2	B2	2B
4-Chloro-*o*-phenylenediamine		95-83-0	RCHAS-E	4.6 E-6	1.6 E-2	NC	2B
p-Chloro-*o*-toluidine		95-69-2	RCHAS-E	7.7 E-5	2.7 E-1	NC	2A
Chromium (hexavalent)	(inhalation)	18540-29-9	TAC	1.5 E-1	5.1 E+2	A	1
	(oral)		RCHAS-S		4.2 E-1		
Chrysene[BaP]	(inhalation)	218-01-9	TAC	1.1 E-5	3.9 E-2	B2	3
	(oral)				1.2 E-1		
Creosote		8001-58-9	ATES	*	*	B1	2A
p-Cresidine		120-71-8	RCHAS-E	4.3 E-5	1.5 E-1	NC	2B
Cupferron		135-20-6	RCHAS-E	6.3 E-5	2.2 E-1	NC	NC
2,4-Diaminoanisole		615-05-4	RCHAS-E	6.6 E-6	2.3 E-2	NC	2B
2,4-Diaminotoluene		95-80-7	RCHAS-E	1.1 E-3	4.0 E+0	NC	2B
Dibenz[*a,h*]acridine[BaP]	(inhalation)	226-36-8	TAC	1.1 E-4	3.9 E-1	NC	2B
	(oral)				1.2 E+0		
Dibenz[*a,j*]acridine[BaP]		224-42-0	TAC	1.1 E-4	3.9 E-1	NC	2B
					1.2 E+0		
Dibenz[*a,h*]anthracene[BaP]	(inhalation)	53-70-3	TAC	3.9 E-4	1.4 E+0	B2	2A
	(oral)		RCHAS-S		4.1 E+0		
Dibenzo[*a,e*]pyrene[BaP]	(inhalation)	192-65-4	TAC	1.1 E-3	3.9 E+0	NC	2B
	(oral)				1.2 E+1		
Dibenzo[*a,h*]pyrene[BaP]	(inhalation)	189-64-0	TAC	1.1 E-2	3.9 E+1	NC	2B
	(oral)				1.2 E+2		
Dibenzo[*a,i*]pyrene[BaP]	(inhalation)	189-55-9	TAC	1.1 E-2	3.9 E+1	NC	2B
	(oral)				1.2 E+2		
Dibenzo[*a,l*]pyrene[BaP]	(inhalation)	191-30-0	TAC	1.1 E-2	3.9 E+1	NC	2B
	(oral)				1.2 E+2		
7H-Dibenzo[*c,g*]carbazole[BaP]	(inhalation)	194-59-2	TAC	1.1 E-3	3.9 E+0	NC	2B
	(oral)				1.2 E+1		

Footnotes

A	see Appendix A
BaP	see benzo[*a*]pyrene TAC document
C	see Appendix C
L	pending Air Resources Board approval
NA	not available
NC	not classified
#	$[100\ PCM\ fibers/m^3]^{-1}$; see Appendix D
*	can be calculated using PEF factors contained in the benzo[a]pyrene TAC document

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RCHAS-E	Expedited Proposition 65 document, OEHHA
ATES	Air Toxicology and Epidemiology Section document, OEHHA
PETS	Pesticide and Environmental Toxicology Section document, OEHHA

Hot Spots Unit Risk and Cancer Potency Values

Chemical		Chemical Abstract Service (CAS) Number	Source	Unit Risk $(\mu g/m^3)^{-1}$	Slope Factor $(mg/kg\text{-}day)^{-1}$	US EPA Class[C]	IARC Class[C]
1,2-Dibromo-3-chloropropane		96-12-8	RCHAS-S	2.0 E-3	7.0 E+0	NC	2B
1,4-Dichlorobenzene		106-46-7	RCHAS-S	1.1 E-5	4.0 E-2	NC	2B
3,3'-Dichlorobenzidine		91-94-1	RCHAS-S	3.4 E-4	1.2 E+0	B2	2B
1,1-Dichloroethane		75-34-3	RCHAS-E	1.6 E-6	5.7 E-3	C	NC
Diethylhexylphthalate		117-81-7	PETS	2.4 E-6	8.4 E-3	B2	2B
p-Dimethylaminoazobenzene		60-11-7	RCHAS-E	1.3 E-3	4.6 E+0	NC	2B
7,12-Dimethylbenz[*a*]anthracene[BaP]	(inhalation)	57-97-6	TAC	2.4 E-2	8.4 E+1	NC	NC
	(oral)		RCHAS-S		2.5 E+2		
1,6-Dinitropyrene[BaP]	(inhalation)	4239-76-48	TAC	1.1 E-2	3.9 E+1	NC	2B
	(oral)				1.2 E+2		
1,8-Dinitropyrene[BaP]	(inhalation)	4239-76-59	TAC	1.1 E-3	3.9 E+0	NC	2B
	(oral)				1.2 E+1		
2,4-Dinitrotoluene		121-14-2	RCHAS-S	8.9 E-5	3.1 E-1	NC	2B
1,4-Dioxane		123-91-1	RCHAS-S	7.7 E-6	2.7 E-2	B2	2B
Epichlorohydrin		106-89-8	RCHAS-S	2.3 E-5	8.0 E-2	B2	2A
Ethylene dibromide		106-93-4	TAC	7.1 E-5	2.5 E-1	B2	2A
Ethylene dichloride		107-06-2	TAC	2.2 E-5	7.0 E-2	B2	2B
Ethylene oxide		75-21-8	TAC	8.8 E-5	3.1 E-1	NC	1
Ethylene thiourea		96-45-7	RCHAS-E	1.3 E-5	4.5 E-2	UR	2B
Formaldehyde		50-00-0	TAC	6.0 E-6	2.1 E-2	B1	2A
Hexachlorobenzene		118-74-1	RCHAS-S	5.1 E-4	1.8 E+0	B2	2B
Hexachlorocyclohexanes (technical grade)		608-73-1	RCHAS-S	1.1 E-3	4.0 E+0	B2	2B
Hydrazine		302-01-2	IRIS	4.9 E-3	1.7 E+1	B2	2B
Indeno[1,2,3-*cd*]pyrene[BaP]	(inhalation)	193-39-5	TAC	1.1 E-4	3.9 E-1	B2	2B
	(oral)				1.2 E+0		
Lead and lead compounds[L]	(inhalation)	7439-92-1	TAC	1.2 E-5	4.2 E-2	B2	2B
	(oral)				8.5 E-3		
Lindane		58-89-9	RCHAS-S	3.1 E-4	1.1 E+0	NC	2B
3-Methylcholanthrene[BaP]	(inhalation)	56-49-5	TAC	2.1 E-3	7.4 E+0	NC	NC
	(oral)		RCHAS-S		2.2 E+1		
5-Methylchrysene[BaP]	(inhalation)	3697-24-3	TAC	1.1 E-3	3.9 E+0	NC	2B
	(oral)				1.2 E+1		
4, 4'-Methylene bis(2-chloroaniline) (MOCA)		101-14-4	RCHAS-E	4.3 E-4	1.5 E+0	NC	2A
Methylene chloride		75-09-2	TAC	1.0 E-6	3.5 E-3	B2	2B
4,4'-Methylenedianiline		101-77-9	RCHAS-E	4.6 E-4	1.6 E+0	NC	2B
Michler's ketone		90-94-8	RCHAS-E	2.5 E-4	8.6 E-1	NC	NC
Nickel compounds		7440-02-0	TAC	2.6 E-4	9.1 E-1	A	1
5-Nitroacenaphthene[BaP]	(inhalation)	602-87-9	TAC	1.1 E-5	3.9 E-2	NC	2B
	(oral)		RCHAS-S		1.3 E-1		

Footnotes

A	see Appendix A
BaP	see benzo[*a*]pyrene TAC document
C	see Appendix C
L	pending Air Resources Board approval
NA	not available
NC	not classified
#	$[100\ PCM\ fibers/m^3]^{-1}$; see Appendix D
*	can be calculated using PEF factors contained in the benzo[a]pyrene TAC document

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ATES	Air Toxicology and Epidemiology Section document, OEHHA
PETS	Pesticide and Environmental Toxicology Section document, OEHHA

Hot Spots Unit Risk and Cancer Potency Values

Chemical		Chemical Abstract Service (CAS) Number	Source	Unit Risk $(\mu g/m^3)^{-1}$	Slope Factor $(mg/kg\text{-}day)^{-1}$	US EPA Class[C]	IARC Class[C]
6-Nitrochrysene[BaP]	(inhalation) (oral)	7496-02-8	TAC	1.1 E-2	3.9 E+1 1.2 E+2	NC	2B
2-Nitrofluorene[BaP]	(inhalation) (oral)	607-57-8	TAC	1.1 E-5	3.9 E-2 1.3 E-1	NC	2B
1-Nitropyrene[BaP]	(inhalation) (oral)	5522-43-0	TAC	1.1 E-4	3.9 E-1 1.2 E+0	NC	2B
4-Nitropyrene[BaP]	(inhalation) (oral)	57835-92-4	TAC	1.1 E-4	3.9 E-1 1.2 E+0	NC	2B
N-Nitroso-n-dibutylamine		924-16-3	RCHAS-S	1.1 E-1	3.1 E-3	B2	2B
N-Nitroso-N-methylethylamine		10595-95-6	IRIS	6.3 E -3	3.7 E+0	B2	2B
N-Nitrosodi-*n*-propylamine		621-64-7	IRIS	2.0 E-3	7.0 E+0	B2	2B
N-Nitrosodiethylamine		55-18-5	RCHAS-S	1.0 E-2	3.6 E+1	B2	2A
N-Nitrosodimethylamine		62-75-9	RCHAS-S	4.6 E-3	1.6 E+1	B2	2A
N-Nitrosodiphenylamine		86-30-6	RCHAS-S	2.6 E-6	9.0 E-3	B2	3
p-Nitrosodiphenylamine		156-10-5	RCHAS-E	6.3 E-6	2.2 E-2	NC	3
N-Nitrosomorpholine		59-89-2	RCHAS-E	1.9 E-3	6.7 E+0	NC	2B
N-Nitrosopiperidine		100-75-4	RCHAS-E	2.7 E-3	9.4 E+0	NC	2B
N-Nitrosopyrrolidine		930-55-2	IRIS	6.0 E-4	2.1 E+0	B2	2B
Pentachlorophenol		87-86-5	RCHAS-S	5.1 E-6	1.8 E-2	B2	2B
Perchloroethylene		127-18-4	TAC	5.9 E-6	2.1 E-2	NC	2B
Polychlorinated biphenyls (PCBs)		1336-36-3	RCHAS-S	2.2 E-3	7.7 E+0	B2	2A
Potassium bromate		7758-01-2	RCHAS-E	1.4 E-4	4.9 E-1	NC	2B
1,3-Propane sultone		1120-71-4	RCHAS-E	6.9 E-4	2.4 E+0	NC	2B
Propylene oxide		75-56-9	IRIS	3.7 E-6	2.4 E-1	B2	2B
1,1,2,2-Tetrachloroethane		79-34-5	IRIS	5.8 E-5	2.0 E-1	C	3
Thioacetamide		62-55-5	RCHAS-E	1.7 E-3	6.1 E+1	NC	2B
2,4-Toluene diisocyanate		584-84-9	RCHAS-E	1.1 E-5	3.9 E-2	NC	2B
2,6-Toluene diisocyanate		91-08-7	RCHAS-E	1.1 E-5	3.9 E-2	NC	2B
1,1,2-Trichloroethane (vinyl trichloride)		79-00-5	IRIS	1.6 E-5	5.7 E-2	C	3
Trichloroethylene		79-01-6	TAC	2.0 E-6	1.0 E-2	NC	3
2,4,6-Trichlorophenol		88-06-2	RCHAS-S	2.0 E-5	7.0 E-2	B2	2B
Urethane		51-79-6	RCHAS-S	2.9 E-4	1.0 E+0	NC	2B
Vinyl chloride		75-01-4	TAC	7.8 E-5	2.7 E-1	NC	1

Footnotes

A	see Appendix A
BaP	see benzo[*a*]pyrene TAC document
C	see Appendix C
L	pending Air Resources Board approval
NA	not available
NC	not classified
#	[100 PCM fibers/m^3]$^{-1}$; see Appendix D
*	can be calculated using PEF factors contained in the benzo[a]pyrene TAC document

Source Key

TAC	Toxic Air Contaminant document, Office of Environmental Health Hazard Assessment (OEHHA)
RCHAS-S	Standard Proposition 65 document, OEHHA
IRIS	Integrated Risk Information System, U.S. Environmental Protection Agency (US EPA)
RCHAS-E	Expedited Proposition 65 document, OEHHA
ATES	Air Toxicology and Epidemiology Section document, OEHHA
PETS	Pesticide and Environmental Toxicology Section document, OEHHA

Selection of Cancer Potency Values

In some instances, several governmental organizations have calculated cancer potency values for the same chemical. The sources for unit risk and cancer potency values included in the Technical Support Document (TSD) for Determining Cancer Potency Factors were generally chosen in the following hierarchical order for the reasons described below:

1. Toxic Air Contaminant documents (Air Toxicology and Epidemiology Section, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency (Cal/EPA))

2. Standard Proposition 65 documents (Reproductive and Cancer Hazard Assessment Section, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency)

3. Integrated Risk Information System (IRIS) documents (Office of Health and Environmental Assessment, U.S. Environmental Protection Agency)

4. Expedited Proposition 65 documents (Reproductive and Cancer Hazard Assessment Section, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency)

5. Air Toxicology and Epidemiology Section (ATES) documents (Air Toxicology and Epidemiology Section, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency)

6. Pesticides and Environmental Toxicology Section (PETS) documents (Pesticides and Environmental Toxicology Section, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency)

All the cancer potency value sources listed above generally follow the recommendations of the National Research Council on cancer risk assessment (NRC, 1983, 1994). The hierarchy of choice listed here gives preference to sources which include external peer review and public comment procedures for publishing cancer potency values. Additional weight of consideration was given to the most recent derivations using the latest data sets and scientific methodology. The publication procedure for Toxic Air Contaminant documents includes a public comment period and review by the Air Resources Board's Scientific Review Panel (SRP) before adoption by the Air Resources Board of the California Environmental Protection Agency (Cal/EPA). Furthermore, a petition procedure is available to initiate TAC document review and revision if required because of new or previously unconsidered toxicity data. The standard Proposition 65 document adoption procedure included a public comment and external peer review by the Proposition 65 Scientific Advisory Panel. The expedited Proposition 65 document adoption procedure includes a public comment period. IRIS documents do not receive public comment or external peer review, but do undergo extensive intraagency review at US EPA and must be approved by the Carcinogen Risk Assessment Verification Endeavor Work Group (CRAVE).

Additional ATES and PETS documents have not received public comment or external peer review, but have undergone extensive Cal/EPA intraagency review.

Cancer Risk Assessment Methodologies

United States Environmental Protection Agency (US EPA)

US EPA carcinogen risk assessment procedures are generally described in Anderson *et al*. (1983) and "Guidelines for Carcinogen Risk Assessment" (US EPA, 1986), and are used in the calculation of cancer potency values listed on the Integrated Risk Information System (IRIS) (Office of Health and Environmental Assessment). US EPA states that cancer risk estimates based on adequate human epidemiologic data are preferred if available over estimates based on animal data.

US EPA Calculation of Carcinogenic Potency Based on Animal Data

The procedures used to extrapolate low-dose human cancer risk from animal carcinogenicity data generally assume that most agents that cause cancer also damage DNA, and that the quantal type of biological response characteristic of mutagenesis is associated with a linear non-threshold dose-response relationship. US EPA states that the risk assessments made with this model should be regarded as conservative, representing the most plausible upper limit for the risk. The mathematical expression used by US EPA to describe the linear non-threshold dose-response relationship at low doses is the linearized multistage model developed by Crump (1980). This model is capable of fitting almost any monotonically increasing dose-response data, and incorporates a procedure for estimating the largest possible linear slope at low extrapolated doses that is consistent with the data at all experimental dose levels.

The linearized multistage model has the form

$P(d) = 1 - \exp[- (q_0 + q_1 d + q_2 d^2 + \cdots + q_k d^k)]$, where $P(d)$ = lifetime risk (probability) of cancer at dose d, $q_i > 0$, and $i = 0, 1, 2, ..., k$

Equivalently, $A(d) = 1 - \exp [- (q_1 d + q_2 d^2 + \cdots + q_k d^k)]$, where $A(d) = \dfrac{P(d) - P(0)}{1 - P(0)}$ is the extra risk over background at dose d. The point estimate of the coefficients q_i; $i = 0, 1,2, ..., k$; and therefore the extra risk function A(d) at any given dose d is calculated by maximizing the likelihood function of the data.

US EPA uses updated versions of the computer program GLOBAL79 developed by Crump and Watson (1979) to calculate the point estimate and the 95% upper confidence limit of the extra risk $A(d)$. Upper 95% upper confidence limits on the extra risk and lower 95% confidence limits on the dose producing a given risk are determined from a 95% upper confidence limit q_1^* on a parameter q_1. When $q_1 \neq 0$, at low doses the extra risk $A(d)$ has approximately the form $A(d) = q_1^* * d$. This term is a 95% upper confidence limit on the extra risk and R / q_1^* is an approximate 95% lower confidence limit on the dose producing an extra risk of R. The upper limit of q_1^* is calculated by increasing q_1 to a value q_1^* such that when the log-likelihood is

remaximized subject to this fixed value q^* for the linear coefficient, the resulting maximum value of the log-likelihood L_1 satisfies the equation $2(L_0 - L_1) = 2.70554$, where L_0 is the maximum value of the log-likelihood function and 2.70554 is the cumulative 90% point of the chi-square distribution with one degree of freedom, corresponding to a 95% upper limit (one-sided). This method of calculating the upper confidence limit for the extra risk $A(d)$ is a modification of the Crump (1980) model. The upper confidence limit for the extra risk calculated at very low doses is always linear with dose. The slope q_1^* is taken as an upper bound of the potency of the chemical in inducing cancer at low doses.

In fitting the dose-response model, the number of terms in the polynomial $g(d)$ equals $(h - 1)$, where h is the number of experimental dose groups (including the control group). If the model does not sufficiently fit the data, data from the highest dose are deleted and the model is refitted to the remaining data. This process is continued until an acceptable fit to the remaining data is accomplished. For purposes of determining if a fit is acceptable, the chi-square

$$x^2 = \sum_{i=1}^{h} \frac{(X_i - N_i P_i)^2}{N_i P_i (1 - P_i)}$$

is calculated, where N_i is the number of animals in the i^{th} dose group, x_i is the number of animals in the i^{th} dose group with a tumor response, P_i is the probability of a response in the i^{th} dose group estimated by fitting the multistage model to the data, and h is the number of remaining groups. The fit is unacceptable when chi-square (X^2) is larger than the cumulative 99% point of the chi-square distribution with f degrees of freedom, where f is the number of dose groups minus the number of non-zero multistage coefficients.

US EPA separates tumor incidence data according to organ sites or tumor types. The incidence of benign and malignant tumors is combined whenever scientifically defensible. US EPA considers this incidence combination scientifically defensible unless the benign tumors are not considered to have the potential to progress to the associated malignancies of the same histogenic origin. The primary comparison in carcinogenicity evaluation is tumor response in dosed animals as compared to contemporary matched control animals. However, US EPA states that historical control data could be used along with concurrent control data in the evaluation of carcinogenic responses, and notes that for the evaluation of rare tumors, even small tumor responses may be significant compared to historical data. If several data sets (dose and tumor incidence) are available (different animal species, strains, sexes, exposure levels, exposure routes) for a particular chemical, the data set used in the model is the set where the incidence is statistically significantly higher than the control for at least one test dose level and/or where the tumor incidence rate shows a statistically significant trend with respect to dose level. The data set generating the highest lifetime cancer risk estimate (q_1^*) is chosen where appropriate. An example of an inappropriate data set would be a set which generates an artifactually high risk estimate because of a very small number of animals used. If there are 2 or more data sets of comparable size for a particular chemical that are identical with respect to species, strain, sex and tumor sites, the geometric mean of q_1^* estimated from each of those data sets is used for risk estimation. The geometric mean of numbers $A_1, A_2, \ldots, A_m$ is defined as $A_1 * A_2 * \ldots * A_m)^{1/m}$. US EPA assumes that mg/surface area/day is an equivalent dose between species. Surface area is

further assumed to be proportional to the 2/3 power of the weight of the animal in question. Equivalent dose is therefore computed using the following relationship:

$$d = \frac{1_e * m}{L_e * W^{2/3}}$$

where L_e = experimental duration, l_e = exposure duration, m = average dose (mg/day) and W = average animal weight. Default average body weights for humans, rats and mice are 70, 0.35 and 0.03 kg, respectively.

Exposure data expressed as ppm in the diet are generally converted to mg/day using the relationship m = ppm * F * r, where ppm is parts per million of the chemical in the diet, F is the weight of the food consumed per day in kg, and r is the absorption fraction (assumed to be 1 in the absence of data indicating otherwise). A proportionality exists between the weight of food consumed, calories required, animal surface area, and the 2/3 power of the animal weight, so that:

$$m \propto \text{ppm} * W^{2/3} * r, \text{ or } \quad \frac{m}{rW^{2/3}} \propto \text{ppm}$$

The relationship could lead to the assumption that dietary ppm is an equivalent exposure between species. However, US EPA believes that this assumption is not justified, since the calories/kg food consumed by humans is significantly different from that consumed by laboratory animals (primarily due to differences in moisture content). US EPA uses an empirically derived food factor, $f = F/W$, which is the fraction of a species' body weight consumed per day as food. The f values for humans, rats and mice used by US EPA are 0.028, 0.05 and 0.13, respectively. Dietary exposures expressed as concentrations in ppm are converted to mg/surface area using the following relationship:

$$\frac{m}{r * W^{2/3}} = \frac{\text{ppm} * F}{W^{2/3}} = \frac{\text{ppm} * f * W}{W^{2/3}} = \text{ppm} * f * W^{2/3}$$

Exposures expressed as mg/kg/day ($m/Wr = s$) are converted to mg/surface area using the relationship:

$$\frac{m}{rW^{2/3}} = s * W^{2/3}$$

The calculation of dose when exposure is via inhalation can be performed for cases where 1) the chemical is either a completely water-soluble gas or aerosol and is absorbed proportionally to the amount of inspired air, or 2) where the chemical is a partly water-soluble gas which reaches an equilibrium between the inspired air and body compartments. After equilibrium is attained, the rate of absorption is proportional to metabolic rate, which is proportional to the rate of oxygen consumption, which is related to surface area.

Exposure expressed as mg/day to completely water-soluble gas or aerosols can be calculated using the expression $m = I * v * r$, where I is the inspiration rate/day in m^3, v is the concentration of the chemical in air (mg/m^3), and r is the absorption fraction (assumed to be the same for all species in the absence of data to the contrary; usually 1). For humans, the default inspiration rate of 20 m^3 has been adopted. Inspiration rates for 113 g rats and 25 g mice have been reported to be 105 and 34.5 liters/day, respectively. Surface area proportionality can be used to determine inspiration rate for rats and mice of other weights; for mice, $I = 0.0345\ (W / 0.025)^{2/3}\ m^3$/day; for rats, $I = 0.105\ (W / 0.113)^{2/3}\ m^3$/day. The empirical factors for air intake/kg/day (i) for humans, rats and mice are 0.29, 0.64 and 1.3, respectively. Equivalent exposures in mg/surface area can be calculated using the relationship:

$$\frac{m}{W^{2/3}} = \frac{Ivr}{W^{2/3}} = \frac{iWvr}{W^{2/3}} = iW^{1/3}vr$$

Exposure expressed as mg/day to partly water-soluble gases is proportional to surface area and to the solubility of the gas in body fluids (expressed as an absorption coefficient r for that gas). Equivalent exposures in mg/surface area can be calculated using the relationships $m = kW^{2/3} * v * r$, and $d = m/W^{2/3} = kvr$. The further assumption is made that in the case of route-to-route extrapolations (e.g., where animal exposure is via the oral route, and human exposure is via inhalation, or vice versa), unless pharmacokinetic data to the contrary exist, absorption is equal by either exposure route.

Adjustments are made for experimental exposure durations which are less than the lifetime of the test animal; the slope q_1^* is increased by the factor $(L/L_e)^3$, where L is the normal lifespan of the experimental animal and L_e is the duration of the experiment. This assumes that if the average dose d is continued, the age-specific rate of cancer will continue to increase as a constant function of the background rate. US EPA states that age-specific rates for humans increase by at least the 2nd power of the age, and often by a considerably higher power, leading to an expectation of an increase in the cumulative tumor rate, and therefore q_1^* , to increase by at least the 3rd power of age. If the slope q_1^* is calculated at age L_e, it would be expected that if the experiment was continued for the full lifespan L at the same average dose, the slope q_1^* would have been increased by at least $(L/L_e)^3$.

US EPA Calculation of Carcinogenic Potency Based on Human Data

US EPA states that existing human epidemiologic studies with sufficiently valid exposure characterization are always used in evaluating the cancer potency of a chemical. If they show a carcinogenic effect, the data are analyzed to provide an estimate of the linear dependence of cancer rates on lifetime cancer dose (equivalent to the factor q_1^*). If no carcinogenic effect is demonstrated and carcinogenicity has been demonstrated in animals, then it is assumed that a risk does exist, but it is smaller than could have been observed in the epidemiologic study. An upper limit of cancer incidence is calculated assuming that the true incidence is just below the level of detection in the cohort studied, which is largely determined by the cohort size. Whenever possible, human data are used in preference to animal data. In human epidemiologic studies, the response is measured as the relative risk of the exposed cohort of individuals compared to the

control group. The excess risk ($R(X)$ - 1, where $R(X)$ is relative risk) is assumed to be proportional to the lifetime average exposure X, and to be the same for all ages. The carcinogenic potency is equal to $[R(X) - 1]/X$ multiplied by the lifetime risk at that site in the general population. The confidence limit for the excess risk is not usually calculated due to the difficulty in accounting for inherent uncertainty in the data (exposure and cancer response).

Office of Environmental Health Hazard Assessment (OEHHA), California Environmental Protection Agency

Office of Environmental Health Hazard Assessment cancer risk assessment procedures are outlined in "Guidelines for Chemical Carcinogen Risk Assessments and their Scientific Rationale" (referred to below as the Guidelines) (CDHS, 1985). These procedures are generally used in generating Toxic Air Contaminant (TAC) cancer potency values (Air Toxicology and Epidemiology Section, Office of Environmental Health Hazard Assessment), standard Proposition 65 cancer potency values (Reproductive and Cancer Hazard Assessment Section (RCHAS), Office of Environmental Health Hazard Assessment) and ATES cancer potency values (Air Toxicology and Epidemiology Section, Office of Environmental Health Hazard Assessment). Expedited Proposition 65 cancer potency values (Reproductive and Cancer Hazard Assessment Section (RCHAS), Office of Environmental Health Hazard Assessment) depart somewhat from those procedures and are discussed separately below.

OEHHA cancer risk assessment methodology (CDHS, 1985) generally resembles that used by US EPA (Anderson *et al*., 1983; US EPA, 1986). The Guidelines state that both animal and human data, when available, should be part of the dose-response assessment.

OEHHA Calculation of Carcinogenic Potency Based on Animal Data

The procedures used to extrapolate low-dose human cancer risk from animal carcinogenicity data assume that a carcinogenic change induced in a cell is transmitted to successive generations of cells descended from that cell, and that the initial change in the cell is an alteration (e.g. mutation, rearrangement, etc.) in the cellular DNA. Non-threshold models are used to extrapolate to low-dose human cancer risk from animal carcinogenicity data.

Several models proposed for extrapolating low-dose human cancer risk from animal carcinogenicity data are described in the Guidelines; these models include the Mantel-Bryan method (log-probit model), the one-hit model, the linearized multistage model, the gamma multihit model, and a number of time-to-tumor models. The Guidelines state that time-to-tumor models (i.e., a Weibull model) should be used for low-dose extrapolation in all cases where supporting data are available and particularly when survival is poor due to competing toxicity. However, the Guidelines also note the difficulty of determining the actual response times in an experiment; internal tumors are generally difficult to detect in live animals and their presence is usually detected only at necropsy. Additionally, use of these models often requires making the determination of whether a tumor was the cause of death, or was found only coincidentally at necropsy when death was due to other causes. Further, competing causes of death, such as chemical toxicity, may decrease the observed time-to-tumor for nonlethal cancers by allowing

earlier necropsy of animals in higher dose groups. The linearized multistage model is noted as being an appropriate method for dose extrapolation in most cases, with the primary exception being a situation in which sufficient empirical data are available to indicate a dose-response curve of a "quasi-threshold" type (e.g., flat for two or three dose levels, then curving sharply upwards). In this case, the linearized multistage model may underestimate the number of stages and overestimate the low-dose risks. In this case, the gamma multihit model is suggested as being a potential alternative. The Mantel-Bryan model is described as having little biological basis as applied to carcinogenesis, and being likely to underestimate risks at low doses. The Guidelines state that this model should not be used for low dose extrapolation.

The Guidelines state that both animal and human data, when available, should be part of the dose-response assessment. Low-dose extrapolation of human cancer risk from animal carcinogenicity data is generally based on the most sensitive site, species and study demonstrating carcinogenicity of a particular chemical, unless other evidence indicates that the data set in question is not appropriate for use. Where both benign and malignant tumors are induced at the same site and the malignant tumors are significantly increased, the data on both types of tumors may be combined to form the basis for risk assessment. Pharmacokinetic data on chemical metabolism, effective dose at target site, or species differences between laboratory test animals and humans are considered in dose-response assessments when they are available. In performing exposure scaling from animals to humans, the "surface area" correction (correcting by the 2/3 power of body weight) is used unless specific data indicates that this should not be done. The Guidelines assume that in the absence of evidence to the contrary, chemicals that cause cancer after exposure by ingestion will also cause cancer after exposure by inhalation, and vice versa. Unit risk factors $(\mu g/m^3)^{-1}$ are calculated from cancer potency factors $(mg/kg\text{-}day)^{-1}$ using the following relationship:

$$UR = \frac{CPF * 20\ m^3}{70\ kg\ *\ CV}$$

where UR is the unit risk, CPF is the cancer potency factor, 70 kg is the reference human body weight, 20 m^3 is the reference human inspiration rate/day, and CV is the conversion factor from mg to µg (= 1000). The Guidelines recommend the use of the linearized 95% upper confidence interval of risk as a dose-response assessment guideline.

OEHHA Calculation of Carcinogenic Potency Based on Human Data

Human epidemiologic studies with adequate exposure characterization are used to evaluate the cancer potency of a chemical. If they show a carcinogenic effect, the data are analyzed to provide an estimate of the linear dependence of cancer rates on lifetime cancer dose. The Guidelines state that with continuous exposure, age-specific incidence continues to increase as a power function (e.g., t^4) of the elapsed time since initial exposure. Lifetime risks can be estimated by applying this power function to the observed data and extrapolating beyond the actual followup period. The specific approaches used in OEHHA risk assessments based on human epidemiologic studies vary on a case by case basis; examples of the methods used can be

observed in the Toxic Air Contaminant documents (these documents are referenced in Appendix B).

Reproductive And Cancer Hazard Assessment Section (RCHAS), Office of Environmental Health Hazard Evaluation (OEHHA), California Environmental Protection Agency (Cal/EPA): Expedited Proposition 65 Cancer Risk Assessment Methodology

Expedited cancer potency values developed for several agents listed as carcinogens under Proposition 65 (California Health and Safety Code 25249.5 et seq.) by RCHAS were derived from selected data sets of the Carcinogenic Potency Database (CPDB) of Gold *et al.* (1984, 1986, 1987, 1989, 1990) using default procedures specified in the administrative regulations for Proposition 65 (Title 22 California Code of Regulations [CCR] 12703). OEHHA hazard assessments usually describe all relevant data on the carcinogenicity (including dose-response characteristics) of the chemical under examination, followed by an evaluation of any pharmacokinetic and mechanistic (e.g. genotoxicity) data. An evaluation of the data set for the chemical may indicate that adjustments in target dose estimates or use of a dose response model different from the default are appropriate. The procedure used by RCHAS to derive expedited Proposition 65 cancer potency values differs from the usual methodology in two ways. First, it relies on cancer dose response data evaluated and extracted from the original literature by Gold *et al.*. Second, the choice of a linearized multistage model for generating cancer potency values is automatic, and pharmacokinetic adjustments are not performed. The methods used by RCHAS to develop expedited cancer potency values incorporate the following assumptions:

1. The dose response relationship for carcinogenic effects in the most sensitive species tested is representative of that in humans.

2. Observed experimental results can be extrapolated across species by use of the interspecies factor based on "surface area scaling."

3. The dose to the tissue giving rise to a tumor is assumed to be proportional to the administered dose.

4. The linearized multistage polynomial model can be used to extrapolate potency outside the range of experimental observations to yield estimates of "low" dose potency.

5. Cancer hazard increases with the third power of age.

The Carcinogenic Potency Database of Gold *et al.* (1984, 1986, 1987, 1989, 1990) contains the results of more than 4000 chronic laboratory animal experiments on 1050 chemicals by combining published literature with the results of Federal chemical testing programs (Technical Reports from the Carcinogenesis Bioassay Program of the National Cancer Institute (NCI)/National Toxicology Program (NTP) published prior to June 1987). The published literature was searched (Gold *et* al., 1984) through the period December 1986 for carcinogenicity bioassays; the search included the Public Health Service publication “Survey of Compounds Which Have Been Tested for Carcinogenic Activity” (1948-1973 and 1978), monographs on

chemical carcinogens prepared by the International Agency for Research on Cancer (IARC) and Current Contents. Also searched were Carcinogenesis Abstracts and the following journals: British Journal of Cancer, Cancer Letters, Cancer Research, Carcinogenesis, Chemosphere, Environmental Health Perspectives, European Journal of Cancer, Food and Cosmetics Toxicology, Gann, International Journal of Cancer, Journal of Cancer Research and Clinical Oncology (formerly Zeitschrift fur Krebsforschung und Klinische Onkologie), Journal of Environmental Pathology and Toxicology, Journal of Toxicology and Environmental Health, Journal of the National Cancer Institute, and Toxicology and Applied Pharmacology. Studies were included in the database if they met the following conditions:

1. The test animals were mammals.

2. Chemical exposure was started early in life (100 days of age or less for hamsters, mice and rats).

3. Route of administration was via the diet, drinking water, gavage, inhalation, intravenous injection or intraperitoneal injection.

4. The test chemical was administered alone (not in combination with other chemicals).

5. Chemical exposure was chronic, with not more than 7 days between exposures.

6. The experiment duration was at least half the standard lifespan for the species used.

7. The study design included a control group and at least 5 animals/exposure group.

8. No surgical interventions were performed.

9. Pathology data were reported for the number of animals with tumors (not total number of tumors).

10. All results reported were original data (not analysis of data reported by other authors).

Included in their data set tabulations are estimates of average doses used in the bioassay, resulting tumor incidences for each of the dose levels employed for sites where significant responses were observed, dosing period, length of study and histopathology. Average daily dose levels were calculated assuming 100% absorption. Dose calculations follow procedures similar to those of Cal/EPA and US EPA; details on methods used and standard values for animal lifespans, body weights, and diet, water and air intake are listed in Gold *et al.* (1984). RCHAS (1992) reviewed the quality assurance, literature review, and control procedures used in compiling the data and found them to be sufficient for use in an expedited procedure. Cancer potency estimates were derived by applying the mathematical approach described in the section below to dose response data in the Gold *et al.* database. The following criteria were used for data selection:

1. Data sets with statistically significant increases in cancer incidence with dose ($p \leq 0.05$) were used. (If the authors of the bioassay report considered a statistically significant result to be unrelated to the exposure to the carcinogen, the associated data set was not used.)

2. Data sets were not selected if the endpoint was specified as "all tumor-bearing animals" or results were from a combination of unrelated tissues and tumors.

3. When several studies were available, and one study stood out as being of higher quality due to numbers of dose groups, magnitude of the dose applied, duration of study, or other factors, the higher quality study was chosen as the basis for potency calculation if study results were consistent with those of the other bioassays listed.

4. When there were multiple studies of similar quality in the sensitive species, the geometric mean of potencies derived from these studies was taken. If the same experimentalists tested two sexes of the same species/strain under the same laboratory conditions, and no other adequate studies were available for that species, the data set for the more sensitive sex was selected.

5. Potency was derived from data sets that tabulate malignant tumors, combined malignant and benign tumors, or tumors that would have likely progressed to malignancy.

Cancer potency was defined as the slope of the dose response curve at low doses. Following the default approach, this slope was estimated from the dose response data collected at high doses and assumed to hold at very low doses. The Crump linearized multistage polynomial (Crump *et al.*, 1977) was fit to animal bioassay data:

$$\text{Probability of cancer} = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + ...)]$$

Cancer potency was estimated from the upper 95 % confidence bound on the linear coefficient q_1, which is termed q_1^*.

For a given chemical, the model was fit to a number of data sets. As discussed in the section above, the default was to select the data for the most sensitive target organ in the most sensitive species and sex, unless data indicated that this was inappropriate. Deviations from this default occur, for example, when there are several bioassays or large differences exist between potency values calculated from available data sets.

Carcinogenicity bioassays using mice and/or rats will often use an exposure duration of approximately two years. For standard risk assessments, this is the assumed lifespan for these species. Animals in experiments of shorter duration are at a lower risk of developing tumors than those in the standard bioassay; thus potency is underestimated unless an adjustment for experimental duration is made. In estimating potency, short duration of an experiment was taken into account by multiplying q_1^* by a correction factor equal to the cube of the ratio of the assumed standard lifespan of the animal to the duration of the experiment (T_e). This assumes

that the cancer hazard would have increased with the third power of the age of the animals had they lived longer:

$$q_{animal} = q_1^* * (104 \text{ weeks}/T_e)^3$$

In some cases excess mortality may occur during a bioassay, and the number of initial animals subject to late occurring tumors may be significantly reduced. In such situations, the above described procedure can, at times, significantly underestimate potency. A time-dependent model fit to individual animal data (i.e., the data set with the tumor status and time of death for each animal under study) may provide better potency estimates. When Gold *et al.* indicated that survival was poor for a selected data set, a time-dependent analysis was attempted if the required data were available in the Tox Risk (Crump *et al.*, 1991) data base. The Weibull multistage model (Weibull-in-time; multistage-in-dose) was fit to the individual animal data.

To estimate human cancer potency, q_{animal} values derived from bioassay data were multiplied by an interspecies scaling factor (K; the ratio of human body weight (bw_h) to test animal body weight (bw_a), taken to the 1/3 power (Anderson *et al.*, 1983)):

$$K = (bw_h/bw_a)^{1/3}$$

Thus, cancer potency = $q_{human} = K * q_{animal}$

Chemical-specific Descriptions of Cancer Potency Value Derivations

Information summaries for chemicals whose cancer potency values were obtained from standard or expedited Proposition 65 documents, Integrated Risk Information System (IRIS) documents, Health Effects Assessment Summary Table (HEAST) entries, Air Toxicology and Epidemiology (ATES) documents and Pesticides and Environmental Toxicology (PETS) documents follow this section. Complete information summaries for chemicals with cancer potency values obtained from Toxic Air Contaminant documents are contained in those documents and are not included below. These documents have all undergone public comment and review by the SRP, and are available from the California Air Resources Board (these documents are referenced in Appendix B).

How the Technical Support Document for Determining Cancer Potency Values (TSD) Addresses the RAAC Committee Recommendations

The Technical Support Document for Determining Cancer Potency Values (TSD), which was drafted concurrently with the release of the Risk Assessment Advisory Committee (RAAC) draft final report, follows the RAAC report recommendations quite closely. The table below lists the applicable RAAC report recommendations and the ways in which the TSD adheres to those recommendations.

RAAC recommendation	TSD implementation
An internal Cal/EPA working group should be established whose specific charge is to insure agency-wide consistency and harmonization.	Cal/EPA-generated cancer potency values contained in the TSD have been reviewed by the Standards and Criteria Work Group, an internal Cal/EPA working group, for consistency and harmonization. The cancer potency factors in the TSD are the same as those in the Standards and Criteria Workgroup's document entitled "Criteria for Carcinogens".
Cal/EPA should develop a formalized program for peer review.	The TSD will be peer reviewed by an advisory committee of scientists from outside State government (the Air Resources Board's Scientific Review Panel) using a formalized process.
Cal/EPA should seek early input into the risk assessment process from risk managers and from external stakeholders. The Agency should identify effective and efficient mechanisms for participation by the general public and interested stakeholders and apply these throughout the Agency.	The TSD has been reviewed by Cal/EPA risk assessors and the Air Quality Management and Air Pollution Control Districts and will be distributed to interested parties, including external stakeholders, for public comment. The Cal/EPA cancer potency factors have already undergone stakeholder, public and peer review in their respective programs prior to their inclusion in this document.
The Committee recommends that Cal/EPA consider an approach in conducting chemical risk assessments that balances the level of effort and resources with the importance of the risk assessment.	The TSD has optimized use of OEHHA resources by developing a decision hierarchy which permits utilization of previously developed Cal/EPA and US EPA cancer potency factors.
"Cal/EPA should endeavor to develop future risk assessments in concert with US EPA, especially for high volume and/or high risk compounds. Before Cal/EPA conducts an independent risk assessment for a substance, it should first review any existing US EPA risk assessment."	The TSD has incorporated US EPA cancer potency factors listed in IRIS (as shown in the Unit Risk and Cancer Potency Factors Table of the TSD) where appropriate. In other cases California-developed information has been used if it supersedes US EPA information, or addresses compounds still awaiting consideration by US EPA.

Appendix E of the TSD provides US EPA IRIS unit risk and cancer potency values for all chemicals listed in the TSD. Appendix F presents the ratios of the California-developed unit risk values used in the Unit Risk and Cancer Potency Factors Table of the TSD with the corresponding unit risk values (where available) listed in IRIS.

Comparison of Hot Spots Cancer Unit Risk Values Which Differ From Corresponding US EPA IRIS Cancer Unit Risk Values

Chemical	OEHHA RA performed considering US EPA RA information	OEHHA RA based on newer study compared to the corresponding US EPA RA	OEHHA RA received external peer review	OEHHA RA received public comment	Are OEHHA and US EPA unit risk values essentially similar?[A]	Resolution of the differences between the OEHHA and US EPA RAs will require additional research
Acetaldehyde	yes	no	yes	yes	yes	no
Acrylonitrile	yes	no	yes	yes	no	no
Arsenic (inorganic, inhalation)	yes	yes	yes	yes	yes	no
Asbestos	no[B]	no	yes	yes	no	no
Benzene	yes	no	yes	yes	no	no
Benzidine	yes	no	yes	yes	no	no
Bis(2-chloroethyl) ether	yes	no	yes	yes	no	no
Bis(chloromethyl)ether	yes	no	yes	yes	no	no
1,3-Butadiene	yes	yes	yes	yes	yes	no
Cadmium (and compounds)	yes	no	yes	yes	no	no
Carbon tetrachloride	yes	no	yes	yes	no	no
Chloroform	yes	yes	yes	yes	no	no
Chromium (hexavalent)	yes	no	yes	yes	no	yes
3,3'-Dichlorobenzidine	yes	no	yes	yes	no	no
1,4-Dioxane	yes	no	yes	yes	no	no
Epichlorohydrin	yes	no	yes	yes	no	no
Ethylene dibromide	yes	no	yes	yes	no	no
Ethylene dichloride	yes	no	yes	yes	yes	no
Formaldehyde	yes	yes	yes	yes	yes	no
Hexachlorobenzene	yes	yes	yes	yes	yes	no
Hexachlorocyclohexanes (technical grade)	yes	no	yes	yes	no	no
Methylene chloride	yes	no	yes	yes	no	yes
Nickel compounds	yes	yes	yes	yes	yes	no
N-Nitroso-n-dibutylamine	yes	no	yes	yes	no	no
N-Nitrosodiethylamine	yes	no	yes	yes	no	no
N-Nitrosodimethylamine	yes	no	yes	yes	no	no
N-Nitrosodiphenylamine	yes	no	yes	yes	yes	no
Pentachlorophenol	yes	no	yes	yes	no	yes
2,4,6-Trichlorophenol	yes	no	yes	yes	no	yes

Abbreviations

RA: risk assessment CDHS: California Department of Health Services

Footnotes

A: Chemicals having a Hot Spots/IRIS unit risk ratio of greater than 0.5 but less than 2.

B: Both the CDHS RA and the US EPA RA were published in the same year.

The above table describes differences between OEHHA and US EPA risk assessments in cases where US EPA IRIS unit risk values exist for chemicals that have an OEHHA unit risk value listed in the TSD Unit Risk And Cancer Potency Value Table. In addition to the chemicals listed above, the Unit Risk and Cancer Potency Table proposes OEHHA adoption of 12 US EPA IRIS cancer unit risk values. OEHHA/IRIS unit risk value ratios are listed in Appendix F.

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ACETAMIDE

CAS No: 60-35-5

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	59.07
Boiling point	222 °C
Melting point	81 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 2.416 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.0 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 7.0 E-2 $(mg/kg\text{-}day)^{-1}$
[Male Fischer 344 rat liver tumor data (Fleischman *et* al., 1980), contained in Gold *et al.* database (1990), expedited Proposition 65 methodology (Cal/EPA, 1992), cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of acetamide on humans are known to exist.

Animal Studies

Dessau and Jackson (1955) exposed 5 Rockland albino rats to acetamide by gavage (4 g/kg body weight/day in distilled water) for 205 days. One animal developed an hepatocellular adenoma.

Male Wistar rats (25/group) were fed diet containing 0, 1.25, 2.5 or 5% acetamide for 1 year (Jackson and Dessau, 1961). One rat/group was sacrificed at monthly intervals; the remaining animals were sacrificed at 1 year. Liver tumors (described as trabecular carcinomas or adenocarcinomas) were seen in 0/25, 4/24, 6/22 and 1/18 animals from the control, low, medium and high dose groups. In the same study, a group of 50 male Wistar rats were fed a diet containing 5% acetamide for 1 year. One animal was killed weekly for 26 weeks, after which 1 animal was killed every other week. Liver tumors (trabecular carcinomas or adenocarcinomas) were observed in 4/48 animals treated for 38-42 weeks, compared to 0/43 in controls.

Male Wistar rats were fed control diet (15 animals), or diets containing 2.5% acetamide (40 animals), 2.5% acetamide + 5.6% L-arginine L-glutamate (40 animals), or 5.6% L-arginine L-glutamate (15 animals) for 1 year. Hepatomas were observed in 2/8 animals fed acetamide alone and killed after 1 year; 7/16 animals fed acetamide alone for 1 year followed by control diet for 3 months also developed liver tumors. In contrast, 1/11 animals fed diet containing acetamide + L-

arginine L-glutamate for 1 year developed hepatomas, and 1/19 animals fed diet containing acetamide + L-arginine L-glutamate for 1 year followed by control diet for 3 months developed hyperplastic liver nodules, but not tumors. No liver tumors were noted in either the control or 5.6% L-arginine L-glutamate treatment groups (Weisburger *et al*., 1969).

Fleischman *et al*.(1980) fed male and female C57BL/6 mice (50/sex/group) and Fischer 344 rats (50/sex/group) a diet containing 1.18% (mice) or 2.36% (mice, rats) acetamide for 365 consecutive days; animals were then fed a control diet for an additional 4 months. Male mice demonstrated a treatment-related increase in hematopoietic tumors, primarily malignant lymphomas; tumor incidence was 7/50 and 7/46 for the low and high dose groups, respectively, compared to 0/95 for the pooled (male and female) control group. Neoplastic nodules and hepatocellular carcinomas were observed in both male and female rats. However, the incidence, speed of onset and frequency of metastases were greater in males (Fleischman et al., 1980). No liver tumors were noted in control animals. Incidence data for hepatocellular carcinomas in F344 rats, the most sensitive species tested, are given in Table 1.

Table 1: Incidence of hepatocellular carcinomas in F344 rats treated with acetamide by dietary administration (Fleischman *et al*., 1980).

Dietary Concentration (%)	Average Dose[1] (mg/kg-day)	Tumor Incidence[2]	
		Male	Female
0	0	0/50	0/49
2.36	710	41/47	33/48

1. Doses as reported by Gold et al. (1984).

2. Decreased survival of treatment group according to Gold et al. (1990) (56% survival at study termination compared to 86% for controls); potency may be an underestimate (Cal/EPA, 1992).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The carcinogenicity bioassay by Fleischman *et al*. (1980) indicated that acetamide causes hematopoietic tumors in male C57BL/6 mice, and hepatocellular carcinomas in male and female Fischer 344 rats. Rats were more sensitive than mice, and male rats were more sensitive than female rats in this study; therefore, the male Fischer 344 rat liver tumor data was used as the basis of a cancer potency factor.

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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ACRYLAMIDE

CAS No: 79-06-1

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	71.08
Boiling point	125°C at 25 mm Hg
Melting point	84.5
Vapor pressure	0.007 mm Hg at 25°C
Air concentration conversion	1 ppm = 2.91 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.3 E-3 $(\mu g/m^3)^{-1}$
Slope Factor: 4.5 E+0 $(mg/kg\text{-}day)^{-1}$
[Calculated by US EPA/IRIS (1988, 1993) from female Fischer 344 rat tumor data (central nervous system, mammary and thyroid glands, uterus, oral cavity) (Johnson *et al*., 1986) using a linearized multistage model, extra risk; adopted by CDHS/RCHAS (1990).]

III. CARCINOGENIC EFFECTS

Human Studies

US EPA (1993) reviewed a study of cancer mortality in workers exposed to acrylamide by Collins (1984). Data from a long duration exposure group (10 individuals) and a short duration/intermittent exposure group (52 individuals) was analyzed using a standardized proportional mortality ratio (SPMR) procedure. No excess mortality for all types of cancer combined was noted in either group. Mortality from lung and central nervous system cancer appeared to be slightly elevated. However, the SPMRs were not significantly different from expected values, due to small group size. US EPA (1993) also noted additional study limitations including underrepresentation of the potential at-risk worker population, incomplete cause of death ascertainment, and incomplete exposure data.

Sobel *et al*. (1986) studied the mortality experience of 371 workers (365 white males, 6 white females) employed in acrylamide monomer production and polymerization operations at the Michigan Division of the Dow Chemical Company from 1955 through 1979. Vital status followup was performed from the date of the first potential exposure to December 31, 1982. Mortality comparisons were made between the cohort and United States white male mortality rates; comparisons were made with a subcohort of workers previously exposed to organic dyes both included and excluded. Slight excesses of mortality from all cancers (11 observed/7.9 expected), digestive tract cancer (4 observed/1.9 expected) and respiratory tract cancer (4 observed/2.9 expected) were observed in the total cohort; these excesses were not observed when the organic dye exposure subcohort was excluded. The authors concluded that the study did not support a relationship between acrylamide exposure and general or specific cancer mortality.

However, US EPA (1988) considers this study insufficient to assess the carcinogenicity of acrylamide in humans because of small cohort size, multiple chemical exposures, limited followup, and short exposure duration (167 cohort members had < 1 year of employment; 109 had 1-4 years of employment).

Animal Studies

Bull *et al*. (1984a) exposed female Sencar mice and male and female A/J mice to acrylamide. Female Sencar mice (40/treatment group) were exposed to 0, 12.5, 25.0 or 50.0 mg/kg body weight acrylamide by gavage, intraperitoneal injection or dermal application. Doses were administered 6 times over a 2 week period; total doses were 0, 75, 150 and 300 mg/kg. Acrylamide was dissolved in distilled water for gavage and intraperitoneal injection administration, and in ethanol for dermal application. Two weeks after the cessation of acrylamide exposure, 1.0 µg 12-*O*-tetradecanoyl-phenol-13-acetate (TPA) dissolved in 0.2 ml acetone was applied to the shaved back of each animal 3 times/week for 20 weeks. A promotion control group was included which received 300 mg/kg acrylamide followed by dermal applications of 0.2 ml acetone on the same treatment schedule and duration as the animals receiving TPA. All animals were sacrificed at 52 weeks, and were evaluated for the presence of skin tumors. Male and female A/J mouse (40/sex/treatment group) acrylamide exposures were conducted at laboratories of the US EPA (Cincinnati, OH) and the Medical College of Ohio (Toledo, OH) (MCO) . Animals exposed at US EPA received acrylamide dissolved in distilled water by gavage 3 times/week for 8 weeks at doses of 0, 6.25, 12.5 or 25 mg/kg. Animals exposed at MCO initially received acrylamide by intraperitoneal injection 3 times/week for 8 weeks at doses of 0, 1, 3, 10, 30 or 60 mg/kg; however, peripheral neuropathy and decreased survival forced treatment termination on the 60 mg/kg group after the 11th injection. An untreated control group was also included. Animals were sacrificed after either 7 months (US EPA) or 6 months (MCO) and examined for lung adenomas. Acrylamide induced skin tumors (squamous cell papillomas and carcinomas) in TPA-promoted female Sencar mice in a dose-dependent manner when administered by gavage, intraperitoneal injection or dermal application. Acrylamide did not induce skin tumors by any route of administration in animals not receiving TPA. Tumor incidence data from female Sencar mice exposed to acrylamide are listed in Table 1.

The incidence of lung adenomas in both male and female A/J mice exposed to acrylamide by either gavage or intraperitoneal injection was significantly increased in a dose-related manner (Bull *et al*., 1984a). Tumor incidence data for animals treated by intraperitoneal injection is listed in Table 2; numerical tumor incidence data for animals exposed to acrylamide by gavage was not listed.

Acrylamide dissolved in water was administered by gavage (0, 75, 150 or 200 mg/kg body weight, divided into 6 equal portions) to female ICR-Swiss mice (40 animals/treatment group) over a 2 week period (Bull *et al*., 1984b). Two weeks after the last acrylamide exposure, the animals were exposed 3 times/week to dermal applications of 2.5 µg TPA for 20 weeks. Another group of 20 animals were exposed to a total dose of 300 mg/kg acrylamide, but received dermal applications of acetone alone. All animals were sacrificed after 52 weeks. Acrylamide caused a

significant dose-related increase in the incidence of skin tumors (papillomas and carcinomas combined). The incidence in animals also receiving TPA was 0/35, 4/34, 4/32 and 13/32 (number of animals with tumors/number of animals examined) for the control, low, mid and high dose groups, respectively; the skin tumor incidence in animals receiving 300 mg/kg acrylamide but not TPA was 10/36. Acrylamide-treated animals also demonstrated a significant dose-related increase in the incidence of lung tumors (alveolar and bronchiolar adenomas and carcinomas). The incidence in animals also receiving TPA was 4/36, 8/34, 6/36 and 11/34 for the control, low, mid and high dose groups, respectively; the lung tumor incidence in animals receiving 300 mg/kg acrylamide but not TPA was 14/36.

Table 1. Skin tumor (squamous cell papillomas and carcinomas) incidence in female Sencar mice exposed to acrylamide (Bull *et al*., 1984a)

Total administered dose[1] (mg/kg body weight)	Route of administration	TPA[2]	Tumor incidence
0	gavage	+	2/40
75		+	12/40
100		+	23/40
300		+	30/40
300		-	0/20
0	intraperitoneal injection	+	0/40
75		+	10/40
100		+	13/40
300		+	21/40
300		-	0/20
0	dermal	+	7/40
75		+	4/40
100		+	11/40
300		+	18/40
300		-	0/20

1. The exposure duration was less than lifetime (2 weeks); the total administered dose listed was not adjusted to reflect a less-than-lifetime exposure.
2. TPA = 12-*O*-tetradecanoyl-phenol-13-acetate

Table 2. Lung adenoma incidence in male and female A/J mice exposed to acrylamide by intraperitoneal injection (Bull *et al*., 1984a)

Dose level[1] (mg/kg body weight)	Percent of animals with tumors	
	males	females
0	13	8
1	50	35
3	38	53
10	59	79
30	93	93

1. The exposure duration was less than lifetime (8 weeks); the dose level listed was not adjusted to reflect a less-than-lifetime exposure.

Robinson *et al*. (1986) exposed female SENCAR, BALB/c, A/J and ICR-Swiss mice (60 mice/strain/treatment group) to a single 50 mg/kg body weight dose of acrylamide by intraperitoneal injection; 2 days later 40 of the 60 mice in each treatment group received 1.0 µg (SENCAR), 2.5 µg (A/J and ICR-Swiss) or 5.0 µg (BALB/c) TPA in 0.2 ml acetone applied dermally 3 times/week for 20 weeks. The remaining 20 mice/strain/treatment group received acetone alone for the same treatment schedule and duration. All animals were sacrificed at 40 weeks, and were only examined for the number of skin papillomas and lung adenomas/animal. Acrylamide induced a significant increase in the number of skin papillomas and lung adenomas per animal in SENCAR mice receiving TPA treatment. The total number of animals bearing tumors was not listed. No significant increase in either tumor type was noted in the other mouse strains tested; tumor data for the animals receiving acrylamide but not TPA was not reported.

Male and female Fischer 344 rats (90/sex/treatment group) were exposed to acrylamide in drinking water for 2 years (Johnson *et al*., 1986). Acrylamide water concentrations were adjusted to provide dosages of 0, 0.01, 0.1, 0.5 or 2 mg/kg body weight/day. Interim sacrifices (10 animals/sex/treatment group) were performed at 6, 12 and 18 months. A maximum tolerated dose (MTD) was achieved based on decreased weight gain, increased mortality during the last 4 months of the study and the appearance of several toxic effects (including peripheral nerve degeneration) in the 2 mg/kg/day group. Increases in the incidences of a number of tumor types were observed in the 2.0 mg/kg/day exposure group animals. An increased incidence of thyroid gland-follicular epithelium tumors was observed in both males and females. In females, increased tumor incidences were noted in the mammary glands, central nervous system, oral tissues, uterus and clitoral gland. An increased incidence of scrotal mesothelioma was noted in males, in both the 2.0 and 0.5 mg/kg/day exposure group; additionally, although not statistically significant, the incidence of scrotal mesothelioma in the 0.1 mg/kg/day group was greater than either the control group or historical control incidences. Male rats in the 2.0 mg/kg/day exposure group also had a significant increase in adrenal pheochromocytomas, and an increased incidence of central nervous system tumors when compared to historical controls but not when compared to concurrent controls. Tumor incidence data is listed in Table 3.

Table 3. Acrylamide-induced tumor incidences in male and female Fischer 344 rats (Johnson *et al*., 1986)

Administered dose (mg/kg/day)	Human equivalent dose[1] (mg/kg/day)	Tumor type	Tumor incidence	
			males	females
0	0	combined central nervous	NA	13/60
0.01	0.001	system (CNS), mammary	NA	18/60
0.1	0.015	gland, oral cavity, thyroid	NA	14/60
0.5	0.076	gland, uterus[2]	NA	21/60
2.0	0.305		NA	46/60
0	0	adrenal pheochromacytomas[3]	3/60	NA
0.01	0.001		7/60	NA
0.1	0.015		7/60	NA
0.5	0.076		5/60	NA
2.0	0.305		10/60	NA
0	0	central nervous system[4]	5/60	1/60
0.01	0.001		2/60	2/60
0.1	0.015		0/60	1/60
0.5	0.076		3/60	1/60
2.0	0.305		8/60	9/60
0	0	oral cavity[5]	6/60	0/60
0.01	0.001		7/60	3/60
0.1	0.015		1/60	2/60
0.5	0.076		5/60	3/60
2.0	0.305		6/60	8/60
0	0	mammary gland[6]	NA	2/60
0.01	0.001		NA	2/60
0.1	0.015		NA	1/60
0.5	0.076		NA	5/58
2.0	0.305		NA	8/61
0	0	scrotal mesotheliomia	3/60	NA
0.01	0.001		0/60	NA
0.1	0.015		7/60	NA
0.5	0.076		11/60	NA
2.0	0.305		10/60	NA
0	0	thyroid[7]	1/60	1/58
0.01	0.001		0/58	0/59
0.1	0.015		2/59	1/59
0.5	0.076		1/59	1/58
2.0	0.305		7/59	5/60
0	0	uterine adenocarcinomas	NA	1/60
0.01	0.001		NA	2/60
0.1	0.015		NA	1/60
0.5	0.076		NA	0/59
2.0	0.305		NA	5/60

1, 2. As calculated by US EPA (1988).

Table 3 (continued). Acrylamide-induced tumor incidences in male and female Fischer 344 rats (Johnson *et al*., 1986)

3. Benign and malignant.
4. Tumors of glial origin or glial proliferation suggestive of early tumor.
5. Squamous cell papillomas and carcinomas.
6. Adenomas and adenocarcinomas.
7. Males: follicular adenomas; females: follicular adenomas and adenocarcinomas.

NA not available

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The studies by Bull *et al*. (1984a, 1984b), Robinson *et al*. (1986) and Johnson *et al*. (1986) indicate that acrylamide is capable of acting as both an initiator and a complete carcinogen in animals. However, only the Johnson *et al*. (1986) study contained a data set suitable for generating a cancer potency factor. Female Sencar mice developing tumors after exposure to acrylamide in the study by Bull *et al*. (1984a) were also additionally exposed to TPA; animals not exposed to TPA did not develop skin tumors. Female A/J mice exposed in that study to acrylamide by either gavage or intraperitoneal injection developed an increased incidence of lung adenomas without requiring TPA exposure. However, the animals were not evaluated for tumor types other than lung adenomas, and numerical tumor incidence data for animals exposed to acrylamide by gavage was not listed. Also, the exposure and observation durations for animals exposed by gavage (8 weeks and 7 months, respectively) and by intraperitoneal injection (8 weeks and 6 months, respectively) were short. Female ICR-Swiss mice exposed to acrylamide by gavage in the study by Bull *et al*. (1984b) were generally also exposed to TPA; only one exposure group was included which received acrylamide (300 mg/kg) but not TPA. Additionally, the exposure duration was only 2 weeks and the exposure duration was less than lifetime (52 weeks). In the study by Robinson *et al*. (1986), all animals for which tumor incidence data was reported were exposed to TPA as well as acrylamide. Animals in the Johnson *et al*. (1986) study were exposed to acrylamide alone for the lifetime of the animals, and were comprehensively examined for tumors. For these reasons, tumor incidence data from the Johnson *et al*. (1986) study was used to derive a cancer potency factor for acrylamide.

Methodology

As recommended in the US EPA Guidelines for Carcinogen Risk Assessment (1986), US EPA (1988) pooled tumor incidence data from different tumor sites, under the consideration that risk numbers derived from site-specific tumor incidence data potentially may not be predictive of, and may in fact underestimate, "whole-body" risks that are determined using the pooled individual animal data. The dose-response curves for each sex based on the pooled tumor incidence (benign and malignant) constituted the data sets of choice for risk assessment. Tumors at a particular site were added into the pool only when the tumor site had statistically significantly increased incidence at least at the high dose level (treated vs. control). The female rat was considered to be

the more sensitive sex, as there were significantly increased tumor incidences at a greater number of sites than in the males; the female rat tumor data was therefore used as the basis of a risk estimate. A linearized multistage model (GLOBAL 83) was fitted to the female rat tumor incidence data, and a cancer potency factor (q_1^*) was calculated. Surface area scaling was employed to transform animal cancer potency factors to human cancer potency factors, using the relationship ($q_{human} = q_{animal} * (bw_h / bw_a)^{1/3}$), where q_{human} is the human potency, q_{animal} is the animal potency, and bw_h and bw_a are the human and animal body weights, respectively. Body weight values used for humans and rats were 70 kg and 0.2 kg, respectively. No exposure route adjustment was made to the risk estimates because data exists which indicates that the pharmacokinetics and tissue distribution of acrylamide were not significantly affected by the dose administered or the route of administration (Dearfield *et al*., 1988). US EPA calculated a cancer potency value (q_{human}) of 4.5 E+0 $(mg/kg\text{-}day)^{-1}$. A unit risk factor was then calculated from the cancer potency factor by OEHHA/ATES using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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ACRYLONITRILE

CAS No: 107-13-1

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	53.06
Boiling point	77.3°C
Melting point	-82°C
Vapor pressure	100 mm Hg at 23°C
Air concentration conversion	1 ppm = 2.2 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.9 E-4 $(\mu g/m^3)^{-1}$
Slope Factor: 1.0 E+0 $(mg/kg\text{-}day)^{-1}$
[Human respiratory tract cancer incidence data (O'Berg, 1980), relative risk model (US EPA, 1983), reevaluated by CDHS/RCHAS (1988).]

III. CARCINOGENIC EFFECTS

Human Studies

Cancer incidence and mortality in a cohort of 1345 male workers exposed to acrylonitrile at a E.I. du Pont de Nemours and Co., Inc. textile plant in Camden SC was studied by O'Berg (1980). The study cohort was identified as having had potential exposure to acrylonitrile in the period between plant startup in 1950 and 1966. The 1966 cutoff date allowed for a 10-year follow-up through the end of 1976. Worker exposure levels were assessed qualitatively by the author and a committee of six DuPont employees with long-term experience in the acrylonitrile exposure area; plant environmental monitoring data was not available for the 1950-1966 period. High, moderate and low exposure categories were established. The U.S. Environmental Protection Agency (US EPA) (1983) noted that DuPont representatives agreed that 5, 10 and 20 ppm might be used to represent the low medium and high exposure classification levels. Expected numbers of cancer cases and deaths were calculated from both DuPont corporate data and from the 1969-1971 National Cancer Institute survey data set. However, the author only listed the results of cancer incidence and mortality calculations using the DuPont "control" data set as the source of the expected numbers of cancer cases and mortality; US EPA (1983) stated that the presentation of results based on this control cohort only would ignore the possible effects of other chemicals on the company control cohort. Exposed workers demonstrated 25 cases of all types of cancer, with 20.5 expected. Of these cases, 8 were lung cancer versus 4.4 expected. For workers employed during plant startup (1950-1952) and exposed for at least 6 months, 8 cases of lung cancer were noted vs. 2.6 expected ($p < 0.01$). Most of this excess occurred during the latest followup period (1970-1976) (6 cases of lung cancer vs. 1.5 expected, $p < 0.01$). Total cancer cases in this period were also significantly increased (17 observed, 5.6 expected, $p < 0.01$). Also, a trend was observed correlating increased cancer risk with increased severity of exposure.

Workers in the moderate exposure group with a probable latent period of at least 15 years exhibited 13 cases of cancer of all types vs. 5.5 expected, and 5 cases of lung cancer vs. 1.4 expected ($p < 0.05$).

One potential confounding factor in this study is the lack of controls for tobacco smoking. US EPA (1983) investigated the possible impact of smoking on lung cancer incidence in the O'Berg (1980) study. DuPont provided additional data on 32 of 36 cancer cases reported on in the plant under study (some cases were not in the study cohort) and on smoking data for a matched group of non-cancer cases. Of the 32 cancer cases for which smoking data was available, 22 were cancer types other than lung, and 16 of the non-lung cancer cases (73%) were smokers. Of the matched noncancer controls, 25 (69%) were smokers. US EPA estimated that 70% of the plant population were smokers and 30% nonsmokers, and of the smoker population, 50% were "moderate" smokers and 20% were "heavy" smokers. Based on the assumption that the relative risk of lung cancer for nonsmokers, moderate, and heavy smokers is 1, 10 and 20, respectively, US EPA adjusted the number of expected lung cancer cases in the study cohort to reflect the smoking prevalence data. The number of expected lung cancer cases after adjustment for smoking is 1.61 cases. This is about 15% higher than the 1.4 cases expected without considering smoking differences; however, this adjustment did not substantially alter the significance of the increased prevalence of lung cancer in the workers exposed to acrylonitrile. US EPA (1983) concluded that the observations by O'Berg (1980) of a statistically significant excess of lung cancer in acrylonitrile-exposed workers constitutes significant evidence that acrylonitrile is likely to be a human carcinogen.

A followup to the O'Berg (1980) study was conducted by O'Berg *et al*. (1985). Observations of cancer incidence and mortality for the study cohort of 1345 DuPont workers exposed to acrylonitrile was extended through 1981 for mortality and through 1983 for cancer incidence. Exposed workers demonstrated 43 cases of all types of cancer, with 37.1 expected. Of these cases, 10 were lung cancer versus 4.4 expected. These rates were in excess but were not statistically significant. Additionally, prostate cancer rates were significantly elevated, with 6 cases observed compared to 1.8 cases expected ($p < 0.05$).

Theiss *et al*. (1980) (reviewed by US EPA, 1983) conducted a cohort mortality study of 1469 workers from 12 factories owned by the BASF company in the Federal Republic of Germany (FRG). BASF purchased acrylonitrile during the study period in order to produce styrene-acrylonitrile and acrylonitrile-butadiene-styrene polymers in addition to organic intermediate products. Processing methods differed between factories, and worker exposure data was not available. The study population was defined as all workers employed for over 6 months in acrylonitrile processing from the time of first use of acrylonitrile (approximately 1956) to the study cut-off date of May 15, 1978. The cohort included 1081 German workers and 338 workers of other nationalities. Followup was 98% complete on the German workers, but only 56% complete on the foreign workers. Expected deaths were calculated from mortality rates for the city of Ludwigshafen, the state of Rheinhessen-Pfalz, and the FRG as a whole. An elevated risk of cancer (all types) mortality was noted in the study cohort (27 observed, 20.5 expected based on FRG mortality rates). The study cohort also demonstrated a significantly elevated risk of lung cancer (11 observed, 5.65 expected based on FRG rates, $p < 0.05$; 5.92 expected based on

Rheinhessen-Pfalz rates, $p < 0.05$). An excess significant risk of lung cancer remained after 78 cohort members from one factory who reported "contact with other substances since proven to be carcinogenic" were removed from the calculations (9 observed, 4.37 expected based on FRG mortality rates, $p < 0.05$); additionally, a significant excess risk of lymphatic cancer was seen (4 observed, 1.38 expected based on FRG mortality rates, $p < 0.05$).

US EPA (1983) noted that the members of the study cohort were exposed to a number of other carcinogens, including vinyl chloride, and distillation residues including polycyclic aromatic hydrocarbons, cadmium, ß-napthylamine, dimethyl sulfate and epichlorohydrin. Additionally, tobacco smoking was a potential confounding factor; all lung cancer cases were smokers. However, US EPA also noted that the lung cancer risk associated with exposure to acrylonitrile estimated from this study could actually be an underestimate of the actual risk because 1) combining workers from 12 factories between which acrylonitrile exposure levels varied could have lend to an underestimate of risk due to the inclusion of unexposed or minimally exposed workers; 2) the "healthy worker" effect could have resulted in an underestimate of risk; 3) followup on the relatively youthful cohort was insufficient, and did not allow sufficient latency in the cohort segments most at risk - only 447.1 person-years were accumulated in members over 64 years of age and 4) underascertainment of vital status (12% of the study cohort were lost to followup) may have resulted in an undercount of observed deaths. US EPA concluded that it was possible that exposure to acrylonitrile might be related to the excess risk of lung cancer demonstrated by the study cohort of Theiss *et al*. (1980).

Werner and Carter (1981) studied the mortality of 1111 men who worked in acrylonitrile polymerization and acrylic fiber production (6 plants, located in England, Northern Ireland, Scotland and Wales) from 1950 to 1968; surveillance was continued to the end of 1978. An excess of total cancer deaths was noted (21 observed, 18.6 expected) but was not statistically significant. Expected deaths were calculated from mortality rates from England and Wales combined. Only 68 deaths from all causes had occurred as of the end of 1978; 72.4 were expected. An excess of deaths from all types of cancer combined was noted (21 observed, 18.6 expected), but this excess was not statistically significant. Significant increases in deaths due to stomach cancer were noted in all age groups combined (5 observed, 1.9 expected, $p < 0.05$), with deaths in the 55-64 age group comprising the largest portion of those deaths (3 observed, 0.7 expected, $p < 0.05$). A statistically significant elevated risk of lung cancer was also noted in the 15-44 age group (3 observed, 0.7 expected, $p < 0.05$), but not in other age groups or in all age groups combined. The authors note the lack of acrylonitrile exposure data, including potential differences in exposure levels between the 6 plants surveyed. US EPA (1983) also notes the relatively short followup in the cohort subgroup which would be expected to have incurred the greatest risk, the 158 men having the earliest exposure (during the 1950-1958 period). US EPA (1983) concluded that because of the relative youth of the cohort resulting in a small number of expected deaths, the lack of followup, and the lack of control for smoking, the findings of this study are only suggestive.

A cohort mortality study of 327 white male workers employed for 2 or more years between January 1, 1940 and July 1, 1971 at a rubber manufacturing plant in Akron OH who were potentially exposed to acrylonitrile was conducted by Delzell and Monson (1982). Acrylonitrile

exposure levels were not reported. Cause-specific expected deaths were calculated based on both U.S. age and calendar specific white male mortality and mortality rates for other rubber workers from the same city; however, most results reported in this study used expected deaths calculated using U.S. white male mortality rates. An excess risk of lung cancer mortality was observed when either U.S. mortality rates (9 observed, 5.9 expected) or Akron rubber industry mortality rates (9 observed, 4.7 expected) were used to calculate expected lung cancer deaths. Workers employed for 5-15 years and followed for at least 15 years demonstrated a significantly increased risk of lung cancer (4 observed, 0.8 expected, $p < 0.01$). Cohort members could potentially have been exposed to other chemicals used in the same area (butadiene, styrene, vinyl pyridine). Also, smoking controls were not included. However, US EPA (1983) commented that the possibility that the excess risk of lung cancer demonstrated in this study was due to acrylonitrile exposure could not be dismissed.

Chen *et al*. (1987) examined cancer incidence and mortality in a cohort of 1083 male employees at a E.I. du Pont de Nemours and Co., Inc. textile plant in Waynesboro, VA who were potentially exposed to acrylonitrile in the period 1944-1970. Worker exposure levels were assessed by an Exposure Classification Committee consisting of seven DuPont employees with long-term experience in the acrylonitrile exposure area; plant environmental monitoring data was not available for the 1944-1970 period. High, moderate and low exposure categories were established. Expected numbers of deaths were calculated from both U.S. and DuPont mortality rates; however, the authors only listed the results of cancer incidence and mortality calculations using the DuPont "control" data set as the source of the expected numbers of cancer cases and mortality. No significant increase in incidence was noted for either all types of cancer (37 observed, 36.5 expected) or lung cancer (5 observed, 6.9 expected). However, a significant increase in the incidence of prostate cancer (5 observed, 1.9 expected) was noted; of these, 4 occurred in the 1975-1983 period (0.9 expected).

US EPA (1983) also reviewed several unpublished studies of cancer mortality and/or morbidity potentially caused by acrylonitrile (Kiesselbach *et al*., 1980; Zack, 1980; Gaffey and Strauss, 1981; Herman, 1981; Stallard, 1982). These studies indicated no cancer increase in workers potentially exposed to acrylonitrile. However, US EPA concluded that due to design and methodological deficiencies including short followup, small cohort size and young cohort age, "none of these studies can be cited as adequate evidence that acrylonitrile is not carcinogenic".

Animal Studies

Maltoni *et al*. (1977) (reviewed by US EPA, 1983) exposed male and female Sprague-Dawley rats (30/sex/exposure group) to 0, 5, 10, 20 or 40 ppm acrylonitrile by inhalation for 4 hours/day, 5 days/week for 12 months. The animals were then maintained for the remainder of their lifetime. Slight increases in the incidence of the following tumor types were noted: mammary gland tumors in males and females, nonglandular forestomach tumors in males and skin tumors in females. Tumor incidence data are listed in Table 1.

Table 1. Tumor incidence in male and female Sprague-Dawley rats exposed to acrylonitrile by inhalation (Maltoni *et al*., 1977)

Tumor type	Tumor incidence Acrylonitrile concentration (ppm)				
	0	5	10	20	40
mammary tumors (females)	5/30	10/30	7/30	10/30	7/30
mammary tumors (males)	1/30	0/30	1/30	4/30	4/30
nonglandular forestomach papillomas (males)	0/30	1/30	2/30	0/30	3/30
skin carcinomas (females)	0/30	4/30	1/30	1/30	1/30

The authors claimed that these results indicated a "border-line carcinogenic effect". US EPA (1983) noted that low sensitivity of this study due to the low concentrations of acrylonitrile used and the short duration of acrylonitrile exposure (12 months). Additionally, male and female Sprague-Dawley rats (40/sex/group) were exposed to 0 or 5 mg/kg body weight acrylonitrile by gavage 3 times/week for 52 weeks. On spontaneous death, a moderate increase in the incidence of female rat mammary gland tumors and nonglandular forestomach tumors was noted. US EPA (1983) commented that although the observation period was relatively short (52 weeks) and only a single dose level was used, this study provides additional evidence for the carcinogenicity of acrylonitrile.

A three-generation reproductive study on the effect of acrylonitrile exposure in male and female Charles River rats [CRL:COBS CD (SD) BR] was conducted by Litton-Bionetics, Inc. for the Chemical Manufacturers Association (Beliles *et al*., 1980; reviewed by US EPA, 1983). The rats and their offspring were exposed to drinking water containing 0, 100 or 500 ppm acrylonitrile starting 15 days post-weaning and were mated after 100 days. After delivery of two litters, the animals were exposed to acrylonitrile for approximately 45 weeks. After exposure, all animals in generations F_0, F_1b and F_2b were sacrificed and examined histologically. Second-generation rats in the 500 ppm exposure group demonstrated a significant increase in the incidence of astrocytomas and Zymbal gland tumors. Tumor incidence data are listed in Table 2.

Table 2. Tumor incidence data in Charles River rats during a three-generation reproductive study (Beliles *et al*., 1980)

Tumor type	Generation	Tumor incidence Acrylonitrile dose (ppm)		
		0	100	500
astrocytomas	F_0	0/19	1/20	2/25
	F_1b	0/20	1/19	4/17
	F_2b	0/20	1/20	1/20
Zymbal gland	F_0	0/19	0/20	1/25
	F_1b	0/20	2/19	4/17
	F_2b	0/20	0/20	3/20

Bio/Dynamics Inc. conducted a study on the toxicity and carcinogenicity of acrylonitrile in Sprague-Dawley rats (Bio/Dynamics, 1980a) for the Monsanto Company (St. Louis, MO); the results of this study were subsequently submitted to the US EPA by the Monsanto Company on June 30, 1980. Male and female Sprague-Dawley rats (100/sex/treatment group) were exposed to acrylonitrile in drinking water at concentrations of 0,1, and 100 ppm. Interim sacrifices (10/sex/treatment group) were conducted at 6, 12 and 18 months. The study was terminated at less than 2 years because of low survival rates; males were sacrificed at 22 months and females were sacrificed at 19 months. Statistically significant increases were noted in the incidence of astrocytomas of the brain and spinal cord, adenomas and carcinomas of the Zymbal gland, and nonglandular forestomach squamous cell papillomas and carcinomas in males and females of the 100 ppm group. Tumor incidence data are listed in Table 3.

Table 3. Tumor incidences in male and female Sprague-Dawley rats exposed to acrylonitrile in drinking water (Bio/Dynamics, 1980a)

Tumor type	Dose level (ppm)	Tumor incidence	
		males	females
brain astrocytomas	0	2/98	0/99
	1	3/95	1/100
	100	23/97	32/97
spinal cord astrocytomas	0	NA	0/96
	1	NA	0/99
	100	NA	7/98
Zymbal gland carcinomas	0	1/100	0/99
	1	0/91	0/95
	100	14/93	7/98
nonglandular forestomach papillomas/carcinomas	0	3/98	1/100
	1	3/98	4/99
	100	12/97	7/99

NA - not analyzed

A similar study was conducted by Bio/Dynamics Inc. on the toxicity and carcinogenicity of acrylonitrile in Fischer 344 rats (Bio/Dynamics, 1980b) for the Monsanto Company (St. Louis, MO); the results of this study were subsequently submitted to the US EPA by the Monsanto Company on December 12, 1980. Male and female Fischer 344 rats (100/sex/acrylonitrile treatment group; 200/sex/control group) were exposed to acrylonitrile in the drinking water at concentrations of 0,1, 3, 10, 30 and 100 ppm. Interim sacrifices (10/sex/acrylonitrile treatment group; 20/sex/control group) were conducted at 6, 12 and 18 months. The study was designed to be 24 months in duration; however, because of poor survival, all females were sacrificed at 23 months. Males were continued on study until 26 months, when survival rates comparable to females were achieved. Statistically significant increases were noted in the incidence of astrocytomas of the brain and spinal cord in males (30 and 100 ppm groups) and females (10, 30 and 100 ppm group), adenomas and carcinomas of the Zymbal gland in males (30 and 100 ppm groups) and females (10, 30 and 100 ppm groups), and nonglandular forestomach squamous cell

papillomas and carcinomas in males (3, 10 and 30 ppm groups) and females (30 ppm group). Tumor incidence data are listed in Table 4.

Table 4. Tumor incidences in male and female Fischer 344 rats exposed to acrylonitrile in drinking water (Bio/Dynamics, 1980b)

Tumor type	Dose level (ppm)	Tumor incidence	
		males	females
brain astrocytoma	0	2/200	1/199
	1	2/100	1/100
	3	1/100	2/101
	10	2/100	4/95*
	30	10/99*	6/100*
	100	21/99*	23/98*
spinal cord astrocytoma	0	1/196	1/197
	1	0/99	0/97
	3	0/92	0/99
	10	0/98	1/92*
	30	0/99	0/96
	100	4/93*	1/91
Zymbal gland[1]	0	2/189	0/193
	1	1/97	0/94
	3	0/93	2/92
	10	2/88	4/90*
	30	7/94*	5/94*
	100	16/93*	10/86*
nonglandular forestomach[2]	0	0/199	1/199
	1	1/100	1/100
	3	4/97*	2/100
	10	4/100*	2/97
	30	4/100*	4/100*
	100	1/100	2/97

* Statistically significant at $p < 0.05$

Male and female Sprague-Dawley rats (Spartan strain) (100/sex/group) were exposed to acrylonitrile by gavage at dose levels of 0, 0.1 and 10 mg/kg-day, 5 days/week in a study conducted by Bio/Dynamics Inc. for the Monsanto Company (St. Louis, MO) (Bio/Dynamics, 1980c). Study termination was originally planned for 24 months; however, because only 10 and 13 high dose males and females, respectively, were still alive at 20 months, all surviving animals in all groups were killed during the 20th month to ensure that at least 10 animals/sex/group were available for histopathological examination. Interim sacrifices were performed at 6, 12 and 18 months (10 animals/sex/group). Statistically significant increases in tumor incidence were noted in the following tumor types: brain astrocytomas and Zymbal gland squamous cell carcinomas (high dose males and females), stomach papillomas and carcinomas and intestinal tumors (high

dose males), and mammary gland tumors (high dose females). Tumor incidence data are listed in Table 5.

Table 5. Tumor incidence in male and female Sprague-Dawley rats (Spartan strain) exposed to acrylonitrile by gavage (Bio/Dynamics, 1980c)

Tumor type	Sex	Tumor incidence Dose level (mg/kg-day)		
		0	0.10	10.0
brain astrocytoma	male	2/100	0/97	16/98
	female	1/99	2/100	17/100
spinal cord astrocytoma	male	0/94	0/93	1/97
	female	0/100	0/95	1/99
Zymbal gland squamous cell carcinomas	male	1/96	0/93	10/96
	female	0/85	0/94	9/94
stomach papillomas/carcinomas	male	2/99	6/97	40/99
	female	2/99	4/99	17/99
intestine	male	0/100	1/100	6/100
	female	NA	NA	NA
mammary gland	male	NA	NA	NA
	female	7/101	6/100	22/101

Dow Chemical Company (Midland, MI) performed a study in which male and female Sprague-Dawley rats (48 animals/sex/acrylonitrile exposure group; 80 animals/sex/control group) were exposed to acrylonitrile in drinking water for 2 years (Quast *et al*., 1980a). For the first 21 days of the study, the concentrations used were 0, 35, 85 and 210 ppm; the two higher concentrations were subsequently raised to 100 and 300 ppm. Animals at the highest 2 concentrations demonstrated treatment-related toxicity after 9 months. The mean administered doses of acrylonitrile were calculated to be 0, 3.42, 8.53 and 21.18 mg/kg-day for males and 4.36, 10.76 and 24.97 mg/kg-day for females for the 35, 100 and 300 ppm exposure groups, respectively. All surviving animals were sacrificed at 24 months. Statistically significant increases in tumor incidence were noted for the following tumor types: central nervous system tumors (astrocytomas, gliomas) in males and females (all treatment groups), Zymbal gland adenomas and carcinomas in females (all treatment groups) and males (300 ppm group), nonglandular forestomach squamous cell papillomas and carcinomas in males (all treatment groups) and females (100, 300 ppm groups), tongue squamous cell papillomas and carcinomas in males (all treatment groups) and females (100, 300 ppm groups), mammary gland tumors (benign and malignant) in females (35, 100 ppm groups), and small intestine cystadenocarcinomas in females (100, 300 ppm). Tumor incidence data are listed in Tables 6 and 7.

Table 6. Tumor incidence in male Sprague-Dawley rats exposed to acrylonitrile in drinking water (Quast *et al*., 1980a)

Tumor type	Tumor incidence Acrylonitrile dose level (ppm)			
	0	35	100	300
brain and/or spinal cord[1]	1/80	12/47	22/48	30/48
nonglandular forestomach[2]	0/80	3/46	23/48	39/47
tongue[2]	1/75	2/7	4/9	5/40
Zymbal gland carcinomas	3/80	4/47	3/48	15/48

1. Benign and/or malignant
2. Squamous cell papillomas and/or carcinomas

Table 7. Tumor incidence in female Sprague-Dawley rats exposed to acrylonitrile in drinking water (Quast *et al*., 1980a)

Tumor type	Tumor incidence Acrylonitrile dose level (ppm)			
	0	35	100	300
brain and/or spinal cord[1]	0/80	17/48	22/48	24/48
mammary gland[1]	57/80	42/48	42/48	35/48
nonglandular forestomach[2]	1/80	1/47	12/48	30/48
small intestine[3]	0/80	1/7	4/11	4/48
tongue[2]	0/78	1/5	2/3	12/45
Zymbal gland carcinomas[4]	1/80	5/48	8/48	18/48

1. Benign and/or malignant
2. Squamous cell papillomas and/or carcinomas
3. Mucinous cystadenocarcinomas
4. Adenomas and carcinomas

Male and female Sprague-Dawley rats (Spartan substrain; 100 animals/sex/exposure group) were exposed to acrylonitrile by inhalation in a study conducted by Dow Chemical Company for the Chemical Manufacturers Association (Quast *et al*., 1980b). Study animals were exposed to 0, 20 or 80 ppm of acrylonitrile for 6 hours/day, 5 days/week for 2 years. Statistically significant increases in tumor incidence were noted for the following tumor types: brain and spinal cord glial cell tumors (males and females), mammary gland adenocarcinomas (females), small intestine tumors (benign and malignant) (males), tongue squamous cell papillomas and carcinomas (males) and Zymbal gland tumors (males and females). All tumor incidence increases were noted at the highest concentration tested, 80 ppm, except for brain and spinal cord glial cell tumors in females, which were also noted in the 20 ppm group. Tumor incidence data are listed in Table 8.

Table 8. Tumor incidence in male and female Sprague-Dawley rats exposed to acrylonitrile by inhalation (Quast *et al*., 1980b)

Tumor type	Sex	Tumor incidence Acrylonitrile concentration (ppm)		
		0	20	80
Brain and/or spinal cord glial cell tumors[1]	male	0/100	4/99	22/99
	female	0/100	8/100	21/100
mammary gland adenocarcinomas	female	9/100	8/100	20/100
small intestine[1]	male	2/99	2/20	15/98
Zymbal gland tumors[1]	male	2/100	4/100	11/100
	female	0/100	1/100	11/100

1. Benign and/or malignant

Bigner *et al*. (1987) exposed male and female Fischer 344 rats to acrylonitrile in drinking water. Exposure groups were as follows: 147 males and 153 females exposed to 500 ppm acrylonitrile; 50 males and 50 females exposed to 500 ppm acrylonitrile; 50 males and 50 females exposed to 100 ppm acrylonitrile and 51 males and 49 female control animals. The study was not complete at the time of the report (18 months of exposure); however, they reported 49 primary brain tumors in 215 animals examined from the high dose treatment groups.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Acrylonitrile has been demonstrated to cause cancer in humans (O'Berg, 1980; Werner and Carter, 1981; Delzell and Monson, 1982) and rats; routes of administration for rats include gavage (Bio/Dynamics, 1980c), oral exposure (Beliles *et al*., 1980; Bio/Dynamics, 1980a; Bio/Dynamics, 1980b; Quast *et al*., 1980a; Bigner *et al*. 1987) and inhalation (Maltoni *et al*., 1977; Quast *et al*., 1980b). US EPA (1991) chose to use the O'Berg acrylonitrile occupational exposure study as the basis of derivation of a cancer potency factor for acrylonitrile. This study demonstrated the carcinogenicity of acrylonitrile in a cohort which was sufficiently large and which was followed for an adequate time period. Exposure levels were estimated by representatives of the company employing the study cohort, and a dose-response relationship was observed for the increased cancer risk. This increased risk remained after adjusting for smoking. US EPA (1983) noted that the cancer potency values for acrylonitrile derived from human exposure (O'Berg, 1980) was within one order of magnitude of the cancer potencies derived from rat oral exposure (Bio/Dynamics, 1980a; Bio/Dynamics, 1980b; Quast *et al*., 1980a) and inhalation exposure (Quast *et al*., 1980b) studies.

Methodology

A unit risk (UR) for acrylonitrile was calculated by US EPA (1991) from a relative risk model adjusted for smoking and based on a continuous lifetime equivalent of occupational exposure using the relationship

$$UR = PO\ (R-1) / X = 1.5E\text{-}4/ppb * 0.45\ ppb/\mu g/m^3 = 6.8E\text{-}5\ (\mu g/m^3)^{-1}$$

where: PO = 0.036 = background lifetime probability of death from respiratory cancer
R = 5.0/1.6 = 3.1 = relative risk of respiratory cancer adjusted for smoking (O'Berg, 1980)
X = 500 ppb = continuous equivalent lifetime exposure when 9 years = estimated average exposure duration, and 60 years = estimated maximum possible age at the end of the observation period.

CDHS (1988) reestimated the unit risk factor for acrylonitrile, using the standard lifespan typically assumed by CDHS in risk assessments (70 years) and taking into account the uncertainty in the relative risk estimate. The unit risk was corrected using the following relationship:

$$B^* = B(95) * (70/60)^3$$

where B^* is the unit risk and B(95) is the upper 95% bound on B. This bound was estimated directly by substituting R(95), the upper 95% confidence bound on R, which was found to be 6.6; the second factor $[(70/60)^3]$ was used to extrapolate from a 60 year observation period to a 70 year observation period. The resulting unit risk factor derived was 2.9E-4 $(\mu g/m^3)^{-1}$.

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ALLYL CHLORIDE

CAS No: 107-05-1

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	76.5
Boiling point	44.96°C
Freezing point	-134.5°C
Vapor pressure	295.5 mm Hg at 20°C
Air concentration conversion	1 ppm = 3.13 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 6.0 E-6 $(\mu g/m^3)^{-1}$

Slope Factor: 2.1 E-2 $(mg/kg\text{-}day)^{-1}$

[Linearized multistage model (GLOBAL82) (US EPA, 1986) fitted to NCI (1977) female mouse forestomach tumor data, body weight scaling, adopted by RCHAS/OEHHA (1994), cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

A retrospective cohort mortality study of 1,064 male workers potentially exposed to epichlorohydrin and allyl chloride was conducted by Olsen *et al.* (1994). Study subjects had a minimum of 1 month work experience between 1957-1986 in the production or use of epichlorohydrin and allyl chloride and 1 year total employment duration at Dow Chemical's Texas Operations (Freeport, TX). Job exposure categorization was used to quantify individual exposure based on an evaluation of work practices, production processes and available environmental monitoring data. Vital status follow-up occured through 1989; 66 total deaths were recorded. Standardized mortality ratios (SMR) for all malignant neoplasms or lung cancer were not significantly increased when compared to external (U.S.) or internal (Texas Operations) populations. The authors noted that the study results are limited by the cohort's size, duration of follow-up, relatively few number of observed and expected deaths, and the level of potential epichlorohydrin and allyl chloride exposure.

Animal Studies

Several studies exist on the potential carcinogenicity of allyl chloride in animals; these studies have been reviewed by IARC (1985) and U.S. EPA (1986, 1991).

Male and female $B6C3F_1$ mice and Osborne-Mendel rats (50/group) were exposed to allyl chloride (technical grade; 98% pure) by gavage daily 5 days/week for 78 weeks (NCI, 1977).

Exposure groups for mice were initially 172 or 199 mg/kg body weight for males and 129 or 258 mg/kg for females. Exposure groups for rats were initially 70 or 140 mg/kg body weight for males and 55 or 110 mg/kg for females. Due to toxicity, the initial doses were reduced as the study progressed. Final time-weighted average doses for the 78 week dosing period were 172 and 199 mg/kg/day for male mice; 129 and 258 mg/kg/day for female mice; 57 and 77 mg/kg/day for male rats and 55 and 73 mg/kg/day for female rats. Mice and rats were observed for an additional 13 and 30-33 weeks after the end of the dosing period, respectively. Excessive mortality (50% after 14-38 weeks) was noted in the high-dose rats (both sexes) and male mice. The number of surviving animals in all low-dose groups and high-dose female mice were adequate to evaluate late-developing tumor risk.

No significant increases in tumor incidence were noted in rats. Proliferative nonneoplastic lesions of the stomach were noted in mice of both sexes. In male mice, squamous cell carcinomas of the stomach were found in 0/29 controls (17 vehicle and 12 untreated), 2/36 low-dose animals, and 0/10 high-dose animals (only 10 survived past 52 weeks). In female mice, squamous cell papillomas and carcinomas of the forestomach were found in 0/39 controls (19 vehicle and 20 untreated), 3/47 low-dose animals (2 carcinomas) and 3/45 high-dose animals (no carcinomas). Tumor incidence was not significantly increased compared to controls for either dose group of either sex. However, the combined tumor incidence in females and the carcinoma incidence in low-dose males was significantly increased at both doses compared to historical vehicle controls (1/180 female mice with squamous cell papilloma or carcinoma of the forestomach; 1/180 male mice with squamous cell carcinoma of the forestomach). The authors considered the findings to be strongly suggestive of carcinogenicity in mice because of the rarity of the tumor type involved and because the proliferative lesions demonstrated could be preneoplastic.

Female Ha:ICR Swiss mice (30/group) were exposed to allyl chloride by topical application (31 or 94 mg allyl chloride in 0.2 ml acetone) 3 times/week for 63-85 weeks (Van Duuren *et al*., 1979). Skin tumors were not induced. Lung and stomach papillomas were induced in both the low dose group (3 stomach, 14 lung papillomas) and the high dose group (3 stomach, 12 lung papillomas, 1 glandular stomach adenocarcinoma). Tumor incidences were not significantly increased compared to vehicle or untreated controls (control incidence not reported).

Female Ha:ICR Swiss mice (30/group) received a single dermal application of 94 mg technical grade allyl chloride in 0.2 ml acetone followed 2 weeks later by dermal applications of 5 µg 12-*O*-tetradecanoylphorbol 13-acetate (TPA) 3 times/week for life (median survival 61-82 weeks) (Van Duuren *et al*., 1979). Skin papilloma incidence was significantly increased (7/30 treated animals compared to 6/90 TPA control animals, $p < 0.025$) and time to tumor was decreased (first tumor in treated animals at day 197 compared to day 449 in TPA controls) in allyl chloride -treated animals.

Male and female A/St mice (10/group) received intraperitoneal injections of allyl chloride in tricaprylin 3 times/week for 8 weeks; total doses were 1.2, 2.9 and 5.9 g/kg body weight (Theiss *et al*., 1979). Animals were killed 24 weeks after exposure initiation. The only pathological endpoint examined was the induction of lung tumors as determined by gross examination. The

average number of adenomas/mouse (20 animals/group, both sexes combined) was 0.19 ± 0.1, 0.60 ± 0.2, 0.50 ± 0.27 and 0.60 ± 0.15 in the control, low, medium and high-dose groups, respectively. The incidence of lung adenomas in the high-dose group was significantly increased ($p < 0.05$ by Student's T-test or chi-square test).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The NCI (1978) carcinogenicity bioassay demonstrated a statistically significant increased incidence of squamous cell papillomas and carcinomas of the forestomach in low-dose male mice (2/46, $p < 0.029$) and low-dose (3/47; $p < 0.003$) and high-dose (3/45; $p < 0.003$) female mice when compared to tumor incidences in male (1/180) and female (1/180) historical controls. The female mouse tumor incidence data from this study was chosen as the basis of a cancer potency factor because it demonstrated induction of a rare tumor type by allyl chloride in the most sensitive sex of a sensitive species.

Methodology

Transformed doses were calculated as follows:

transformed dose = experimental dose x (5 days/7 days) x (78 weeks/92 weeks)

Animals were dosed 5 days/week, and the duration of exposure and of the experiment were 78 and 92 weeks, respectively. Experimental doses were 129 and 258 mg/kg/day; transformed doses were 78 and 156 mg/kg/day. A linearized multistage model (GLOBAL82) was then fitted to the tumor incidence data; the resulting unadjusted cancer potency factor (q_1^*) was 1.01 E-3 $(mg/kg/day)^{-1}$. A q_1^* for humans was calculated from the unadjusted q_1^* as follows:

human q_1^* = unadjusted q_1^* x $(70\ kg/0.025\ kg)^{1/3}$ x $(104\ weeks/92\ weeks)^3$
= 2.1 E-2 $(mg/kg/day)^{-1}$

The reference human body weight and the average female mouse weight were 70 kg and 0.025 kg, respectively, and the experiment length and the mouse lifespan were 92 weeks and 104 weeks, respectively. A unit risk factor of 6.0 E-6 $(\mu g/m^3)^{-1}$ was derived from the human q_1^* by OEHHA/ATES using an inspiration rate of 20 m^3/day.

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2-AMINOANTHRAQUINONE

CAS No: 117-79-3

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB (1994) except where noted)

Molecular weight	223.24
Boiling point	sublimes (IARC, 1982)
Melting point	302 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 9.131 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 9.4 E-6 $(\mu g/m^3)^{-1}$
Slope Factor: 3.3 E-2 $(mg/kg\text{-}day)^{-1}$
[Male rat liver tumor data (NCI, 1978), contained in Gold *et al*. database (1984), expedited Proposition 65 methodology (Cal/EPA, 1992), cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of 2-aminoanthraquinone (2-AA) on humans are known to exist.

Animal Studies

Results from the National Cancer Institute (NCI) (1978) feeding study in male and female $B6C3F_1$ mice and Fischer 344 rats are tabulated in Gold *et al*. (1984). 2-Aminoanthraquinone (technical grade, unspecified impurities) was administered in feed to groups of 50 male and 50 female animals of each species. Matched control groups were included for each mouse dose group (50 animals/sex/species). Control groups of 50 male and 25 female rats were also included; these animals were observed for 107-109 weeks. Diet fed to mice contained 5000 or 10000 mg/kg 2-AA; diet fed to female rats contained 2000 mg/kg 2-AA. Diet fed to male rats contained 10000 or 20000 mg/kg 2-AA for the first 10 weeks; this was reduced to 2500 or 5000 mg/kg for the remaining 68 weeks. For rats, NCI reported the time-weighted average dietary concentrations to be 0.69% and 0.35% for high and low dose males, and 0.2% for treated females over a 78-week period. An additional observation period of 28-32 weeks was included after treatment ended. High and low dose mice of both sexes were administered time-weighted average dietary concentrations of 1.0% (over 80 weeks) and 0.5% (over 78 weeks) respectively, and were observed for an additional 15-16 weeks after treatment ended.

At study termination, 82, 78, 94 and 86% of male mice and 78, 76, 88 and 76% of female mice were still alive in the low-dose control, high-dose control, low-dose and high-dose groups,

respectively. In male rats, 54% of the controls, 64% of low-dose and 70% of high-dose animals were alive at the end of the study. Insufficient numbers of female rats survived to the latter portion of the experimental period to permit analysis of late-developing tumors.

High-dose male and female mice demonstrated a significantly increased incidence of hepatocellular carcinomas. Tumor incidence in male mice was 12/46 in low-dose controls, 6/48 in high-dose controls, 20/47 in low-dose animals, and 36/49 ($p < 0.001$) in high-dose animals; in female mice, the frequencies were 4/46, 1/50, 5/47 and 12/47 ($p < 0.001$) (NCI, 1978; Murthy *et* al., 1979). A dose-dependent increase in hepatic neoplastic nodules and hepatocellular carcinomas ($p < 0.001$) was noted in 18/41 low-dose and 18/45 high dose males; tumors were observed in 0/36 control male rats.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The NCI carcinogenicity bioassay of 2-AA indicated that 2-AA induced tumor formation in both rats and mice. The cancer potency value derived is based on the dose-response data for hepatic tumors in the more sensitive sex and species, the male rat (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. The average dose administered to the male rat high-dose group as calculated by Gold *et al*. (1984) was 102 mg/kg/day. Analysis of the data set using the computer program TOX_RISK (Crump et al., 1991) indicated that inclusion of the high dose group resulted in a p-value of ≥ 0.05 based on the chi-square goodness-of-fit test, indicating non-linearity. Following procedures described by US EPA (Anderson *et al*., 1983), the high dose group was excluded from the analysis to correct for the poor fit (Cal/EPA, 1992). A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

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ANILINE

CAS No: 62-53-3

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	93.12
Boiling point	184-186°C
Melting point	-6.3°C
Vapor pressure	0.67 mm Hg at 25°C
Air concentration conversion	1 ppm = 3.82 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.6 E-6 ($\mu g/m^3$)$^{-1}$
Slope Factor: 5.7 E-3 (mg/kg-day)$^{-1}$
[Derived from a cancer potency factor calculated by US EPA/IRIS (1990, 1994) from male rat primary splenic sarcoma incidence data (CIIT, 1982) using a linearized multistage model, extra risk; adopted by CDHS/RCHAS (1990)]

III. CARCINOGENIC EFFECTS

Human Studies

US EPA (1994) reviewed a study that examined the occurrence of bladder tumors in British workers in the chemical dye industry (Case *et al.*, 1954). A group of 4622 men employed for more than 6 months in the United Kingdom chemical industry during the period 1910-1952 were studied. In a subgroup of 1233 men exposed solely to aniline, one death from bladder cancer was observed compared to 0.83 expected from English/Welsh male mortality data. Among the entire group (who had generally been exposed to a number of aromatic amines including napthylamine, benzidine, auramine and aniline; no detailed exposure information was available), 127 deaths from bladder cancer were observed compared to 4.1 expected. The authors concluded that the data provided insufficient evidence to suggest that aniline itself causes bladder tumors.

Animal Studies

Forty-three male and female Osborne-Mendel rats were fed diets containing 330 mg/kg aniline hydrochloride for up to 1032 days (White *et al*., 1948). Hepatomas and splenic sarcomas were noted in 4 and 3 animals, respectively. No control group was included in the study; however, the authors claimed that liver and spleen tumors were rare in the rat strain used in the study.

IARC (1982) reviewed a study by Druckrey (1950) in which rats (random bred, sex unspecified) were exposed to aniline hydrochloride in drinking water (22 mg/rat/day) over their lifetime. Mortality was quite high; 50% mortality occurred at day 450 and 100% mortality at day 750. No tumors were observed in the treated animals; however, only the bladder, liver, spleen and kidney were evaluated for tumors.

Male and female Fischer 344 (F344) rats and B6C3F$_1$ mice were fed diets containing aniline hydrochloride for 103 weeks (NCI, 1978). Rats were fed diets containing 0, 3000 or 6000 mg/kg diet aniline hydrochloride; mice were fed diets containing 0, 6000 or 12000 mg/kg diet aniline hydrochloride. Group sizes were 50/sex/group, except for high dose female mice (n = 49), and control rats (25/sex). Surviving rats and mice were sacrificed at 107-108 and 107 weeks, respectively. No significantly increased treatment-related tumor incidences were noted in treated mice. Male rats demonstrated significantly elevated incidences of hemangiosarcomas in the spleen, as well as fibrosarcomas and sarcomas (not otherwise specified) in multiple organs of the body cavity and spleen. There were also significant dose-related trends in the incidence of hemangiosarcomas, sarcomas or fibrosarcomas and malignant pheochromocytomas. For female rats, a dose-related trend was observed in the incidence of fibrosarcomas and sarcomas in the spleen and in multiple organs of the body cavity. No fibrosarcomas, or sarcomas of the spleen or multiple organs of the body cavity were observed in pooled (249 female and 250 male) control animals. Tumor incidence data is listed in Table 1.

Table 1. Aniline hydrochloride-induced tumor incidence data in male and female Fischer 344 rats (NCI, 1978)

Tumor type	Sex	Tumor incidence aniline hydrochloride dietary concentration (mg/kg diet)		
		0	3000	6000
spleen hemangiosarcoma	male	0/25	19/50	20/46
spleen fibrosarcoma/sarcoma NOS	male	0/25	7/50	9/46
multiple organ fibrosarcoma/sarcoma NOS	male	0/25	2/50	9/48
	female	0/24	1/50	7/50
adrenal pheochromocytomas	male	2/24	6/50	12/44

NOS = not otherwise specified

Hagiwara *et al.* (1980) administered aniline in the diet at a concentration of 300 mg/kg diet to 28 male Wistar rats over a period of 80 weeks. An untreated control group of 28 rats was also included. No significant increase in tumor incidences were observed as a result of aniline exposure. However, the treatment group sizes used were relatively small, and the exposure was relatively low and less than lifetime.

Male and female CD-F rats (130/sex/exposure group) were exposed to aniline hydrochloride in the diet for 2 years at exposure levels of 0, 10, 30 and 100 mg/kg body weight/day (CIIT, 1982). An increased incidence of primary splenic sarcomas was noted in the male 100 mg/kg exposure group (high dose group); stromal hyperplasia and fibrosis of the splenic red pulp, a potential sarcoma precursor lesion, was also observed in high dose males, and to a lesser degree, in high dose females. No fibrosarcomas, stromal sarcomas, capsular sarcomas or hemangiosarcomas were noted in female rats. Tumor incidence data is listed in Table 2.

Table 2: Incidence of splenic tumors in male CD-F rats fed diets containing aniline hydrochloride (CIIT, 1982)

Dietary aniline hydrochloride concentration (approximate) (ppm)	Aniline hydrochloride exposure level (mg/kg body weight/day)	Human equivalent dose[1] $(mg/kg/day)^{-1}$	Tumor incidence[2]
0	0	0	0/64
200	10	1.23	0/90
600	30	3.69	1/90
2000	100	12.29	31/90

1. Calculation of the doses included a correction for the difference in molecular weight of aniline and aniline hydrochloride (compound administered) (US EPA, 1992).
2. Tumor incidence includes fibrosarcomas, stromal sarcomas, capsular sarcomas, and hemangiosarcomas as reported by US EPA (1992).

Syrian golden hamsters (15 male and 15 female) received subcutaneous injections of aniline (521 mg/kg body weight; total dose 9219 mg/kg) for 52 weeks (Hecht et al., 1983). Although mean survival was reduced in the aniline-treated groups, no increase in tumor incidence was observed. However, the experimental exposure was less than lifetime, and the number of exposed animals was small.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Cancer potency values are based on the most sensitive site, species and study demonstrating carcinogenicity of a particular chemical, unless other evidence indicates that the value derived from that data set is not appropriate (CDHS, 1985). Male rat spleen tumor data (CIIT, 1982) was used to generate a cancer potency factor for aniline. Male rats in the high-dose group showed a marked increase in the incidence of splenic tumors (see Table 2). US EPA (1994) also noted the presence of stromal hyperplasia and fibrosis of the splenic red pulp in high-dose males and, to a lesser degree, in females; this may represent a precursor lesion of sarcoma.

Methodology

A linearized multi-stage model (US EPA,1980) was used to calculate a slope factor of 5.7 E-3 $(mg/kg\text{-}day)^{-1}$ from the CIIT (1982) male splenic tumor incidence data. Calculation of the transformed doses for aniline included a correction for the difference in molecular weights of aniline and aniline hydrochloride, the form in which the compound was administered in the NCI and CIIT bioassays. Calculation of the unit risk by OEHHA/ATES from the US EPA slope factor assumed a body weight of 70 kg and an inspiration rate of 20 m^3/day.

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ARSENIC (inorganic)

CAS No. 7440-38-2

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	74.92
Boiling point	615 °C (sublimes)
Melting point	817°C at 28 atm.
Vapor pressure	10 mm Hg at 437°C
Air concentration conversion	not available

II. HEALTH ASSESSMENT VALUES

Unit risk factor: 3.3 E-3 $(\mu g/m^3)^{-1}$
[Human lung cancer data (CDHS, 1990)]
Oral slope factor: 1.5 E+0 $(mg/kg\text{-}day)^{-1}$
[Human skin cancer data (Tseng *et al*., 1968, 1977; US EPA, 1995).]

III. CARCINOGENIC EFFECTS

Human Studies

Inhalation

Several studies have demonstrated that exposure to arsenic by inhalation results in an increased incidence of lung cancer in humans. These studies and the derivation of the inhalation risk factor are described in the Toxic Air Contaminant (TAC) document for inorganic arsenic (CDHS, 1990).

Oral

Chronic exposure to high levels of arsenic in drinking water has been identified as increasing skin cancer incidence in humans (US EPA, 1988, 1995).

In a region on the southwest coast of Taiwan, artesian well water with high arsenic concentrations ranging from 0.01-1.82 ppm had been in use for more than 45 years (Tseng *et al*., 1968, 1977). 40,421 inhabitants of 37 villages of the regions were examined for skin lesions, peripheral vascular disorders and cancers. The study identified 7,418 cases of hyperpigmentation, 2,868 of keratosis (Type A/benign), 428 of skin cancer (squamous cell carcinoma, basal cell carcinoma, *in situ* squamous cell carcinoma, and Type B keratoses/intraepidermal carcinomas) and 360 cases of Blackfoot disease. The incidence rates for keratosis and skin cancer were 183.5 and 10.6/1000, respectively. A control population of 7,500 people did not exhibit any of the above disorders.

The above exposed population was divided into "low", "mid" and "high" exposure groups based upon the well-water arsenic concentration in each village (<0.3, 0.3-0.6, and >0.6 ppm, respectively). A dose-response relationship was identified for the prevalence of skin cancer and Blackfoot disease (no dose-response data was presented for hyperpigmentation and keratosis). The prevalence of both disease was also found to increase with age. Males were found to have higher prevalence rates than females (male to female ratios for skin cancer and Blackfoot disease were 2.9 and 1.3, respectively).

Additional studies of chronic human arsenic exposure resulting in increased skin cancer or internal organ cancer incidence have been identified and reviewed (Fierz, 1965; Borgono and Greiber, 1972; Cebrian *et al*., 1983; Yue-Zhen *et al*., 1985; Chen *et al*., 1985, 1986; reviewed by US EPA, 1988).

Animal Studies

CDHS (1990) has determined that arsenic is a human carcinogen for which carcinogenicity has not been conclusively demonstrated in animals. CDHS (1990) reviewed studies in which animals were exposed to arsenic by inhalation, intratracheal instillation, subcutaneous injection, gavage, or in drinking water. The studies reviewed were generally either negative, or were not conclusive due to methodology or reporting deficiencies.

IV. DERIVATION OF ORAL CANCER POTENCY

Basis for Cancer Potency

US EPA (1995) conducted a review of the available literature and identified the studies by Tseng *et al*. (1968, 1977) as the key references for quantifying ingested arsenic cancer potency. US EPA stated that these studies demonstrate a causal association between arsenic ingestion and an elevated risk of skin cancer. These data were considered reliable for the following reasons: 1) the study and control populations (40,421 and 7,500, respectively) were large enough to provide reliable estimates of the skin cancer incidence rates; 2) a statistically significant elevation in skin cancer incidence in the exposed population compared to the control population was observed many years after first exposure; 3) a pronounced skin cancer dose-response by exposure level was demonstrated; 4) the exposed and control populations were similar in occupational and socioeconomic status, with ingestion of arsenic-contaminated drinking water the only apparent difference between the two groups, and 5) over 70% of the observed skin cancer cases were pathologically confirmed.

Methodology

A generalized multistage model with both linear and quadratic dose assumptions was used to predict the prevalence of skin cancer as a function of arsenic concentration in drinking water (d) and age (t), assuming exposure to a constant dose rate since birth. F(t,d) represents the

probability of developing skin cancer by age t after lifetime exposure to arsenic concentration d. The model used is expressed as follows: $F(t,d) = 1 - \exp[-g(d) H(t)]$, where g(d) is a polynomial in dose with non-negative coefficients, and H(t) is $(t-w)^k$, where k is any positive real number, and $t > w$ for induction time w. The cancer potency calculation was based on skin cancer incidence data for Taiwanese males (Tseng *et al*., 1968) because their skin cancer prevalence rates were higher than the females studied. The calculation was also based on several assumptions listed below.

1. The mortality rate was equal for both diseased (skin cancer) and nondiseased persons.

2. The population composition (with respect to skin cancer risk factors) remained constant over time, implying that there was no cohort effect.

3. Skin cancers were not surgically removed from diseased persons.

The population at risk was classified into 4 age groups (0-19, 20-39, 40-59 and ≥ 60 years of age) and three dose groups (0 - 0.3, 0.3 - 0.6 and > 0.6 ppm drinking water arsenic concentration) for males and females separately from the reported prevalence rates (Tseng *et al*., 1968, 1977) as percentages. The assumption was made that the Taiwanese persons had a constant arsenic exposure from birth, and that males and females consumed 3.5 L and 2 L drinking water/day, respectively. The multistage model was used to predict dose-specific and age-specific skin cancer prevalence rates associated with ingestion of inorganic arsenic. Both linear and quadratic model fitting of the data were conducted. The maximum likelihood estimate (MLE) of skin cancer risk for a 70 kg person drinking 2 L of water/day, adjusted for U.S. population survivorship by life-table analysis, ranged from 1 E-3 to 2 E-3 for an arsenic intake of 1 µg/kg/day. Expressed as a single value, the cancer unit risk for drinking water is 5 E-5 $(\mu g/L)^{-1}$; the corresponding cancer potency value is 1.5 E-0 $(mg/kg/day)^{-1}$.

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BENZIDINE

CAS No: 92-87-5

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	184.2
Boiling point	402°C
Melting point	115-120°C
Vapor pressure	0.0005 mm Hg
Air concentration conversion	1 ppm = 7.53 mg/m^3 @ 25°C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.4 E-1 $(\mu g/m^3)^{-1}$
Slope Factor: 5.0 E+2 $(mg/kg\text{-}day)^{-1}$
[Calculated from a cancer potency factor derived by RCHAS/OEHHA (CDHS, 1988)]

III. CARCINOGENIC EFFECTS

Human Studies

Case *et al.* (1954) examined mortality among British chemical workers exposed to benzidine. Among the population examined (total number not specified), ten deaths were certified as due to bladder cancer. The death rate from bladder cancer in the male Welsh and English population predicts 0.72 deaths from this cause, giving a standard mortality ratio of 13.9 (10/0.72, $p < 0.001$). Non-fatal bladder cancers were also noted among the exposed population.

Mancuso and El-Atar (1967) examined the incidence of urinary tract cancer among 639 male employees of an Ohio plant where benzidine and β-naphthylamine were made, with potential exposure occurring between 1938 and 1939. Six cases of bladder cancer occurred among white workers, giving a population incidence of 204 per 10^5. The expected incidence of bladder cancer among Ohio white males is 4.4 per 10^5. The authors do not present the significance of the change in incidence because of exposure of workers to other compounds.

Zavon *et al.* (1973) conducted a prospective study of workers exposed to benzidine during its manufacture. The authors report on the health surveillance of all 25 employees of a chemical plant who were exposed to benzidine from 3 to 28 years (1930-1958). During the 13 year follow-up period (1957-1970), 11 cases of transitional cell bladder cancer and 2 cases of benign bladder tumors developed. Among the workers with bladder cancers, two also developed kidney carcinomas and one a benign tumor of the kidney. No background tumor incidences were reported. The average exposure duration for workers with tumors was 13.6 years, whereas the

average exposure duration for those without tumors was 8.9 years. Levels of urinary benzidine were measured at the beginning of the follow-up period of the study, with samples taken at the beginning and end of the work day and at the before the work week began. Mean levels were reported to be ~0.01 mg/l before shift, ~0.04 mg/l after shift, and ~0.004 mg/l Monday morning. Quantitative estimates of exposure have been based on these levels. Exposure conditions at the time of the sampling were reported to be representative of conditions in the previous years of plant operation. Air sampling at different locations in the chemical plant showed benzidine concentrations ranged from <0.007 to 17.6 mg/m^3. Potential confounding variables in the study include smoking and exposure to other carcinogens in the work environment such as β-naphthylamine, o-toluidine, and dichlorobenzidine.

Tsuchiya *et al.*(1975) report on the incidence of bladder cancer among 1303 Japanese workers employed in benzidine production or use. Among workers involved in the manufacture of benzidine 61/542 developed bladder cancer. Among workers involved in benzidine use, 11/761 developed bladder cancer. Exposure levels to benzidine and population background incidence of bladder cancer in the Japanese population were not provided in the study. A statistically significant difference in bladder cancer incidence was observed between workers involved in benzidine production versus those involved in benzidine use ($p<10^{-10}$, Fisher's exact test).

Meigs *et al.* (1986) conducted a 30-year follow-up study of 597 male workers at a benzidine manufacturing plant in Connecticut. Workers were categorized based upon time of employment, but benzidine levels were not quantitated. Among workers in the high exposure category (> 2 years of employment) 6/105 developed bladder cancer. Among workers in the medium (6 mo.-2 yrs.) and low (1 day-6 mo.) exposure categories, 1/147 and 0/345 developed bladder cancer, respectively. Connecticut cancer statistics predict 1.77 cases of bladder cancer in an unexposed population of 597 people. A significant difference in incidence between high exposure workers and unexposed populations was found ($p<0.003$).

Animal Studies

Saffioti *et al.*(1967) exposed Syrian Golden hamsters (30/sex/group) for life to 0 or 1000 ppm benzidine or benzidine dihydrochloride in feed, and examined them for evidence of liver tumors. Among animals treated with benzidine, 19/22 males and 6/26 females developed cholangiomatous liver tumors (none in controls). Among animals treated with benzidine dihydrochloride, 10/20 males and 12/27 females developed cholangiomatous liver tumors (none in controls). Liver tumor incidence was found to be significantly elevated in exposed animals in each group ($p<0.001$, Fisher's exact test).

Griswold *et al* .(1968) treated female Sprague-Dawley rats with benzidine by oral gavage. Animals received 1.2 or 2.5 mg/dose (10 animals/group) or 3.5 or 5 mg/dose (20 animals/group) every 3 days, with a total of 10 administrations. After 9 months, surviving animals were examined for tumors. Increased incidence of mammary carcinoma was found in benzidine treated groups, with 5/10, 7/9, and 4/5 showing tumors in the 1.2, 2.5, and 5 mg dose groups, respectively, versus 3/127 in control animals. There were no survivors among the animals receiving 3.5 mg benzidine.

Miakawa and Yoshida (1975) fed female dd strain mice (50/group) diet containing either 0 or 0.2% benzidine for 280 days. Hepatocellular carcinomas were identified in 11 of 32 mice surviving 140 days or more, whereas no hepatocellular carcinomas were reported among control mice. The significance level of the difference in incidence was $p<0.001$ by Fisher's exact test.

Littlefield *et al.*(1984) exposed male and female F_1 generation mice (BALB/c males × C57BL females) to benzidine in drinking water for life (~33 months). Mice from a cross of F_1 generation males and females were also exposed as above . Exposure levels and incidence of hepatocellular carcinomas are presented in Table 1. Significant differences in the incidence of hepatocellular carcinoma were observed in all exposed groups ($p<0.05$, Fisher's exact test). Frith *et al.* (1980) also exposed F_1 and F_2 generation mice (BALB/c males × C57BL/6 females) to 30-400 ppm benzidine dihydrochloride in drinking water for 40, 60, or 80 weeks at which time animals were sacrificed. As in the Littlefield *et al*. (1984) study, animals showed a dose-dependent increase in hepatocellular carcinoma incidence. This effect was also shown to be dependent upon duration of exposure.

Table 1. Incidence of hepatocellular carcinoma in F_1 and F_2 generation mice (BALB/c × C57BL) exposed to benzidine in drinking water (Littlefield *et al*., 1984).

hepatocellular carinoma incidence					
males			females		
exposure level (ppm)	F_1	F_2	exposure level (ppm)	F_1	F_2
0	14/125	17/123	0	3/124	10/125
30	24/119	20/118	20	51/120	54/119
40	30/96	20/95	30	52/95	43/95
60	32/71	23/72	40	45/72	31/71
80	35/71	24/71	60	55/71	37/72
120	61/71	37/71	80	60/69	51/69
160	49/71	32/71	120	64/72	56/72

Vesselinovitch *et al.* (1975) treated male $B6C3F_1$ mice with feed containing 150 ppm benzidine dihydrochloride from weeks 6 to 45 of life. Groups of 50 mice thus treated were sacrificed at 45, 60, 75, or 90 weeks and examined for liver tumors. Hepatoma incidence was reported to be 8/50, 20/50, 31/50, and 35/50, respectively, at successive sacrifice times, while only one hepatoma was found among 98 control animals sacrificed at 90 weeks ($p<0.001$; Fisher's exact test). Among the animals with hepatomas, the incidence of hepatocellular carcinoma was 2/50, 5/50, 14/50, and 24/50, respectively, at the successive sacrifice times.

Two other feeding studies have been conducted. Boyland *et al.* (1954) found cases of hepatocellular carcinoma in rats fed diet containing 0.017% benzidine or benzidine plus tryptophan for life. Inadequate study size, data on controls and poor survival, however, limit the usefulness of this study. Marhold *et al.* (1968) found no tumors in lifetime benzidine feeding study, but poor survival also limits the study's value.

Zabezhinski (1970) exposed 48 albino rats (male and female numbers not specified) to 10-20 mg/m^3 benzidine aerosol for 4 hours/day, 5 days/week for 20 months. Among animals surviving at 13 months, 5/28 developed leukemia (0/21 untreated; p=0.052)

Tumors have also been observed in animals injected subcutaneously with benzidine. They include hepatocellular carcinomas, Zymbal gland tumors and injection-site tumors (Spitz *et al*., 1950; Bonser *et al*, 1956; Pliss, 1964; Prokofjeva, 1971). Intraperitoneal injection of benzidine resulted in the induction of mammary tumors in a single study (Morton *et al*, 1981).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The data presented by Zavon *et al.* (1973) are the only human cancer data appropriate for the development of a cancer potency value for benzidine. The US EPA (1986, 1987, 1988), Allen *et al.* (1987), and CDHS (1988) have each provided estimates of cancer potency based on human data. However, different assumptions made in the calculation of exposure levels has resulted in different estimates of the cancer potency. Potencies derived in these studies assume that cancer risk is proportional to cumulative exposure. Previously, IARC (1982) had suggested that benzidine cancer risk be based on the assumption that the empirical distribution of cumulative incidence rate is a function of the duration of continual exposure. Derivations of cancer potencies from the human data using these different methodologies and exposure assessments are described in the *Methodology* section below.

Cancer potency values have also been derived from animal studies, in particular those of Griswold *et al*. (1968), Miakawa and Yoshida (1975), Saffioti *et al* (1967), and Littlefield *et al*. (1984). Resulting potency estimates were well below those derived from the human data, suggesting humans may be more sensitive to the carcinogenic effects of benzidine, and therefore animal data are not appropriate for use in the establishing a cancer potency value. CDHS has based its benzidine cancer potency value on the human data of Zavon *et al*. (1973) using exposure level assessment modifications of Allen *et al.* (1987) and the methodology of US EPA (1986, 1987, 1988).

Methodology

US EPA (1986, 1987, 1988) made exposure estimates from the Zavon *et al.* study (1973) based upon reported mean urinary concentrations of 0.04 mg/l. Assuming that average body weight is 70 kg, average urinary output is 1.2 l/day, and 1.45% of absorbed benzidine is excreted in the urine, US EPA calculated the average daily dose to be 0.047 mg/kg-day. Adjusting this value for work time exposure, with 11.46 years the average time exposed, 56.5 years the average age of the cohort, and 240 work days per year, final lifetime exposure levels were calculated to be 0.0063 mg/kg-day.

US EPA (1986,1987, 1988) based estimates of cancer potency on the following relationship where p(t) is the probability of developing a tumor in a study of cohort of average age t at the end of the follow-up period (56.5 years) and an average lifespan t_L (71.3 years), exposed to dose level d (0.0063 mg/kg-day), and assuming that background tumor incidence is negligible:

$$\text{cancer potency} = \frac{-\ln(1-p(t))}{(d)(\frac{t}{t_L})^3}$$

With this model, US EPA used total tumor incidence (13/25, both benign and malignant) in its calculation, giving a final potency value of 234 $(\text{mg/kg-day})^{-1}$ (See Table 2). Using the upper 95% confidence bound on the tumor incidence (0.68 vs. 0.52) resulted in a cancer potency value of 363 $(\text{mg/kg-day})^{-1}$.

Using mean urine benzidine concentrations reported at the beginning (0.01 mg/l) and end (0.04 mg/l) of the work day, Allen *et al.* (1987) adjusted benzidine exposure estimates on the assumption of linear increases in urine concentration during the workday and first-order decay during non-work hours. The resulting average urine concentration during workdays was 0.023 mg/l. Based on assumptions that 1.5% of the inhaled benzidine is present in the urine (100% absorption), urinary output is 1.5 l/day, breathing rate is 10 m^3/8-hour work day, and average exposure time of the cohort is 11.24 years, Allen *et al.* (1987) estimated average cumulative dose to be 2.59 mg-yrs/m^3.

Allen *et al.* (1987) calculated potency using this dose value and the malignant tumor incidence only [p(t) = 11/25 = 0.44] with a background tumor incidence factor (α = 0.002; NIH, 1981) and without using a time adjustment factor. That is:

$$\text{cancer potency} = \frac{-\ln[1-p(t)] + \alpha}{d}$$

The resulting estimate of cancer potency from work place exposure was 0.22 $(\text{mg}\cdot\text{yrs/m}^3)^{-1}$. with upper and lower 90% confidence bounds of 0.81 and 0.045 $(\text{mg}\cdot\text{yrs/m}^3)^{-1}$. Cancer potency from continuous lifetime exposure was calculated by assuming 240 workdays of a 365 day year and 10 of 20 m^3/day total air breathed during the workday. Potencies thus expressed are 0.67 $(\text{mg-yr/m}^3)^{-1}$ with upper and lower confidence bounds of 2.5 and 0.14 $(\text{mg-yr/m}^3)^{-1}$. Assumptions of 70 kg body weight, 70 yr lifespan, and 20 m^3/day breathing rate (CDHS, 1988) result in a cancer potency of 160 $(\text{mg/kg-day})^{-1}$ with upper and lower 90% confidence bounds of 600 and 30 $(\text{mg/kg-day})^{-1}$.

An estimate of cancer potency was also made based on a description of cumulative risk described by IARC (1982) (CDHS, 1988). IARC (1982) describe risk based on the assumption that the risk varies linearly with the duration of exposure. IARC (1982) report the data from Zavon *et al.* (1973) show a cumulative bladder tumor incidence of 25% among workers exposed to benzidine for 15 years. Under such an assumption, cancer potency (B) from lifetime (t_L = 70 yrs) exposure

can be based on the following relationship, where $C(t_1)$ is the experimentally derived cumulative tumor incidence (25%) and $d(t_1)$ is the average daily dose at time t_1 (15 years):

$$B = [C(t_1)/d(t_1)] \times [(t_L/t_1)^k]$$

The factor k describes the relationship of time of exposure to potency, in this case k=1 because of the assumption of linear proportionality. From this relationship, CDHS (1988) derived a cancer potency value. Using the average daily dosing derived by Allen *et al.* (0.023 mg/kg-day) and the cumulative incidence data described by IARC (1982), the calculated cancer potency was 50 $(mg/kg\text{-}day)^{-1}$ with upper and lower 95% confidence bounds of 130 and 16 $(mg/kg\text{-}day)^{-1}$ derived from the confidence bounds of the dose.

CDHS (1988) considers the Allen *et al* .(1987) estimation of daily urine concentration of 0.023 mg/l to be the most useful for establishing exposure levels. Assuming 1.5 ℓ/day urinary output, 70 kg body weight, 240 work days per year, and average duration of exposure 11.46 yrs in a cohort of 56.5 yrs average age, lifetime average exposure is 0.0044 mg/kg-day. Using the US EPA (1986, 1987, 1988) methodology and the upper 95% confidence bound on incidence [p(t) = 0.68], the cancer potency is 5.0 E+2 $(mg/kg\text{-}day)^{-1}$.

A unit risk factor of 0.14 $(\mu g/m^3)^{-1}$ was derived by OEHHA/ATES assuming a breathing rate of 20 m^3/day, 70 kg body weight, and 100% fractional absorption of inhaled benzidine.

Table 2. Benzidine cancer potencies derived from Zavon *et al.* (1973).

Source of methodology	Potency $[(mg/kg\text{-}day)^{-1}]$	Upper 95% confidence bound $[(mg/kg\text{-}day)^{-1}]$
US EPA (1986, 1987, 1988)	234	363
Allen *et al.*(1987)	160	600
IARC (1982)*	50	130
CDHS (1988)		500

*Estimate based on IARC methodology using the dosage estimation of Allen *et al.* (1987).

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BENZYL CHLORIDE

CAS No: 100-44-7

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB (1994))

Molecular weight	126.58
Boiling point	179°C
Melting point	-43 to -48°C
Vapor pressure	1 mm Hg at 22°C
Air concentration conversion	1 ppm = 5.26 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 4.9 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 1.7 E-1 $(mg/kg\text{-}day)^{-1}$
[Cancer potency factor derived by US EPA/IRIS (1989) from female rat C-cell thyroid tumor incidence data (Lijinsky, 1986) using a linearized multistage model, extra risk; adopted by RCHAS/CDHS (1991).]

III. CARCINOGENIC EFFECTS

Human Studies
Several studies report on cancer mortality in workers occupationally exposed to benzyl chloride.

Sakabe *et al*. (1976) studied cancer incidences among 41 workers exposed to chemicals including benzyl chloride over 18 years (ending in 1972) in a plant producing benzoyl chloride in Japan. Four cases of cancer were reported among the workers: two fatal cases of lung cancer, one fatal maxillary malignant lymphoma, and one squamous cell carcinoma of the lung (still surviving in 1973). The range of employment duration among the workers with cancer was 6 to 14 years. Both cases of lung cancer were in smokers. The expected number of lung cancer deaths among 41 Japanese males was 0.06. In addition to smoking, another potential confounding factor is the reporting of exposure to other compounds in the work environment including benzotrichloride, benzoyl chloride, toluene, chlorine gas, hydrogen chloride, benzal chloride, and other chlorinated toluenes and polymers. Exposure levels were not quantitated.

Sakabe and Fukuda (1977) also reported on cancer deaths among workers exposed to chemicals including benzyl chloride in another plant involved with the production of benzoyl peroxide and benzoyl chloride between 1952 and 1963. Two lung cancer deaths (one a smoker) were reported. Expected number of deaths and exposure levels were not reported, and workers were also exposed to other chemicals as listed in the description of the study by Sakabe *et al*. (1976).

Sorahan *et al*. (1983) studied cancer mortality among British workers occupationally exposed to a number of compounds including toluene, benzotrichloride, benzoyl chloride, benzyl chloride, and benzal chloride during the course of producing chlorinated toluenes. Five digestive system

cancers and 5 respiratory system cancers were reported among 163 male workers employed more than 6 months between 1961 and 1970. Expected mortality rates from these tumors in England and Wales were 1.24 and 1.78, respectively, and the mortality ratio was significantly elevated. Smoking rates were not reported among the workers. Cumulative exposure and death from any cancer among workers employed before 1951 was shown to be significantly correlated by survival analysis using the Cox Proportional Hazard Model, although this was not the case when entry cohorts were combined.

Wong and Morgan (1984) studied cancer mortality among a cohort of 697 workers employed from 1 to more than 35 years in a chlorination plant in Tennessee. Workers were exposed to benzyl chloride, benzoyl chloride, and benzotrichloride. Deaths from respiratory cancers were reported for 7 workers, 5 of whom were exposed for more than 15 years. Expected mortality for U.S. males in a group of this size was 2.84 deaths (1.32 deaths for the subgroup exposed > 15 years). No data on smoking was reported.

Animal Studies

Lijinsky (1986) treated F344 rats (52/sex/dose) and B6C3F_1 mice (52/sex/dose) with benzyl chloride in corn oil by gavage. The rats were dosed with 0, 15, and 30 mg/kg/day benzyl chloride and mice with 0, 50 and 100 mg/kg/day benzyl chloride, with treatments 3 days/week for 2 years. Animals were histopathologically examined 3-4 weeks after the end of the treatment using the NCI bioassay protocol. Survival in both species was not significantly affected by treatment. The incidence of C-cell adenoma/carcinoma of the thyroid was significantly increased in female rats in the high-dose group compared to control animals (14/52 treated vs. 4/52 control; $p < 0.01$ by Fisher's exact test). In male mice in the high-dose group, significantly increased incidences were found for hemangioma/hemangiocarcinoma (5/52 treated vs. 0/52 control), forestomach carcinoma (8/52 treated vs. 0/51 control) and forestomach carcinoma/papilloma (32/52 treated vs. 0/51 control). In male mice in the low-dose group only, an increased incidence of hepatic carcinoma/adenoma (28/52 treated vs. 17/52 control) was reported. In female mice in the low- and high-dose groups, an increased incidence of forestomach carcinoma/papilloma (5/50 low-dose, 19/51 high-dose vs. 0/52 control) was reported.

Injection-site sarcomas developed in 3 of 14 BD-strain rats administered benzyl chloride in peanut oil subcutaneously weekly for 51 weeks at 40 mg/kg-week and 6 of 8 rats administered 80 mg/kg-week (Druckrey *et al*., 1970). Mean induction time was 500 days.

Poirier *et al*. (1975) treated A/H mice (20/dose) 3 times weekly over 24 weeks intraperitoneally with a total dose of 0.6, 1.5 or 2 g benzyl chloride/kg body weight in tricaprylin. Surviving animals were sacrificed at 24 weeks. Among the survivors, lung tumors were found in 4/15, 7/16, and 2/8 animals, respectively. Animals treated with tricaprylin alone had an average of 0.22 lung tumors/mouse and animals receiving no treatment had 0.21 lung tumors/mouse. The incidence of lung tumors in treated animals was not found to be statistically significant from control animals.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Human studies do not provide adequate data for the development of a cancer potency value because of the presence of confounding factors in the studies (multiple compound exposures, no data on smoking status) and no reporting of exposure levels. The animal study by Lijinsky (1986) showing development of thyroid tumors in female rats, and forestomach papillomas and carcinomas in male and female mice provides data from which cancer potency values can be derived.

Methodology

Cancer potency values were derived by US EPA (1989) from the tumor incidence data presented in the study by Lijinsky (1986). The experimentally administered doses (15 and 30 mg/kg) were converted to time-weighted dosage based on the dosing schedule (3 times/week) and the experimental duration (107.5 weeks). The human equivalent dose (HED) was calculated based on an assumed experimental animal body weight (bw_a) of 0.35 kg and human body weight (bw_h) of 70 kg using the following relationship:

$$\text{HED} = \text{time-weighted dose} \times (bw_a/bw_h)^{1/3}$$

The calculated human equivalent doses in the Lijinsky (1986) study were 1.06 and 2.12 mg/kg-day. A linearized multistage model (CDHS, 1985) was applied to the tumor incidence data for thyroid tumors in female rats (4/52 controls, 8/51 low-dose, 14/52 high-dose), forestomach tumors in male mice (0/51 controls, 5/50 low-dose, 32/52 high-dose) and forestomach tumors in female mice (0/52 controls, 5/50 low-dose, 19/51 high-dose). This resulted in estimations of the upper 95% confidence bound of cancer potency (q_1^*) of 0.17, 0.056, and 0.12 $(\text{mg/kg-day})^{-1}$, respectively. Selection of the cancer potency value is made in the most sensitive species and site; therefore, the cancer potency value [0.17 $(\text{mg/kg-day})^{-1}$] derived from the female rat C-cell thyroid tumor data was chosen.

A unit risk value of 4.9 E-5 $(\mu g/m^3)^{-1}$ was derived by ATES/OEHHA assuming a human breathing rate of 20 m^3/day, a human body weight of 70 kg, and 100% fractional absorption after inhalation exposure.

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BERYLLIUM

CAS No: 7440-41-7

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	9.012
Boiling point	2970°C
Melting point	1287°C
Vapor pressure	10 mm Hg @ 1860°C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.4 E-3 $(\mu g/m^3)^{-1}$
[Calculated by US EPA (1992) from the human inhalation exposure data of Wagoner *et al.* (1980).]

Oral Cancer Potency Factor: 4.3 E+0 $(mg/kg/day)^{-1}$
[Calculated by US EPA (1995) from male and female rat tumor data (Schroeder and Mitchner *et al*., 1975, using a linearized multistage model, extra risk.]

III. CARCINOGENIC EFFECTS

Human Studies

US EPA (1992) reviewed several studies that found increased incidences of lung cancer in beryllium processing workers. A cohort mortality study of 3055 white males employed at a single beryllium processing plant in Pennsylvania with a median duration of employment of 7.2 months demonstrated a statistically significant increased incidence of mortality due to lung cancer in the entire cohort, as well as in the 2068 cohort members followed for 25 years or more since initial employment (Wagoner *et al.*, 1980). Recalculation of the number of expected deaths using 1968-1975 lung cancer mortality data indicated that the increased incidence was significant only among workers followed for 25 years or more (Bayliss, 1980; MacMahon, 1977, 1978), and was not significant when the number of expected deaths was adjusted for smoking (US EPA, 1986).

Earlier studies of workers from the same beryllium processing plant alone or combined with workers from other beryllium plants reported a statistically significant increase in lung cancer mortality (Bayliss and Wagoner, 1977; Mancuso, 1970, 1979, 1980). These studies made no adjustment for smoking and had methodological constraints and deficiencies that precluded their use to establish a causal relationship between beryllium exposure and lung cancer.

Animal Studies

Slight, non-statistically significant increases in cancer incidence (all tumor types) were observed in male Long-Evans rats (52/sex/group) following lifetime exposure to 5 ppm beryllium sulfate administered in the drinking water (Schroeder and Mitchener, 1975a). Tumors were observed in 9/33 treated and 4/26 control rats. High mortality during the study resulting from a pneumonia epidemic at 20 months greatly reduced the power of this study to detect any potential carcinogenic effect of beryllium exposure. A non-statistically significant increase in combined lymphoma and leukemia incidence was observed in female Swiss mice administered 5 ppm beryllium sulfate in drinking water for life (9/52 exposed, 3/47 controls) (Schroeder and Mitchener 1975b).

Male and female Wistar-derived rats were exposed to diet containing beryllium sulfate at concentrations of 0, 5, 50, or 500 ppm for life (Morgareidge et al., 1977). Reticulum cell carcinomas of the lung were observed in 10/49 male control animals, 17/35 low dose animals, 16/40 intermediate dose animals, and 12/39 high dose animals, respectively. Since the results were published only as an abstract, and since no response was seen at the highest dose, these results are considered to be only suggestive for the induction of cancer via this route.

Beryllium and beryllium compounds have been shown to cause statistically significant tumor increases in male and female rhesus monkeys and several strains of rats via inhalation and intratracheal installation, and the induction of osteosarcomas in rabbits by intravenous or intramedullary injection. Studies describing the induction of lung tumors (adenomas, adenocarcinomas) by beryllium via inhalation during exposure periods of up to 72 weeks are listed in Table 1. Intratracheal instillation of beryllium also resulted in the induction of lung tumors and extrapulmonary lymphosarcomas and fibrosarcomas in rats (Groth *et al*., 1980; Ishinishi *et al*., 1980).

Table 1. Induction of lung tumors in animals exposed to beryllium via inhalation

Study	Species/strain	Compound
Reeves et al., 1967	male, female Sprague-Dawley rats	beryllium sulfate
Schepers, 1961	male, female Sherman and Wistar rats	beryllium phosphate, beryllium fluoride, zinc beryllium silicate
Wagner et al., 1969	male Charles River CR-CD rats	beryl ore
Vorwald, 1968	male, female rhesus monkeys	beryllium sulfate

Beryllium compounds were shown to induce osteogenic sarcomas in rabbits by intravenous injection in 12 studies and by intramedullary injection in 4 studies (US EPA, 1991)

V. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Inhalation

Wagoner *et al*. (1980) studied a cohort of 3055 white males employed at a single beryllium processing plant in Pennsylvania (exposed to beryllium metal, oxide or hydroxide) sometime between January 1, 1942 and December 31, 1967 with a median duration of employment of 7.2 months. A significantly increased incidence of mortality due to lung cancer was observed in the entire cohort (47 observed versus 34.29 expected, $p < 0.05$), as well as in the 2068 cohort members followed for 25 years or more since initial employment (20 observed versus 10.79 expected, $p < 0.01$). When the number of expected deaths was recalculated using 1968-1975 lung cancer mortality data, significance was lost for the cohort overall (38.2 expected), but not for the subgroup followed for 25 years or more (13.36 expected, $p \approx 0.05$) (Bayliss, 1980; MacMahon, 1977, 1978). However, significance was lost for the subgroup when the number of expected deaths was adjusted for smoking (14.67 expected) (US EPA, 1986).

The data of Wagoner *et al*. (1980) was used for the quantitation of cancer potency due to inhalation exposure despite study limitations. Human inhalation exposure is usually to beryllium oxide rather than other beryllium salts. Animal studies utilizing beryllium oxide have used intratracheal instillation instead of inhalation exposure. The use of the available human data therefore avoids uncertainties due to cross-species extrapolation, and uses the most relevant route of administration and beryllium species.

Oral

The data of Schroeder and Mitchener (1975a) was used to caculate an oral cancer potency factor for beryllium. Slight, non-statistically significant increases in tumors were observed in male Long-Evans rats administered 5 ppm (0.54 mg/kg/day) beryllium sulfate in drinking water for the duration of their natural lifetime. While this study is limited but the use of only one non-zero dose group, the occurrence of high mortality and unspecified type of and site of the tumors, it was used as the basis of the quantitative estimate because exposure occurred via the most relevant route. Oral risk estimates derived by extrapolation from studies in other species/strains for the intravenous and inhalation routes (also highly uncertain) are within an order of magnitude.

Methodology

Inhalation

A risk assessment was performed based on the occupational exposure study of Wagoner *et al*. (1980). The narrowest range for median exposure that could be obtained on the basis of available information was 100 to 1000 $\mu g/m^3$. Effective dose was calculated by adjusting for the

duration of daily (8 of 24 hours) and annual (240 of 365 days) exposure, and the fraction of the lifetime at risk (time from start of employment to study termination). Smoking-adjusted expected lung cancer deaths were found to range from 13.91 to 14.67 (based on exposure range) compared to 20 observed. Relative risk estimates of 1.36 and 1.44 were calculated and the 95% confidence limits of these estimates used to calculate the lifetime cancer risk (Table 2). These estimates were based on one data set and a range of estimated exposure levels and times. To account for estimation uncertainties, unit risks were derived using two estimates each of concentration, fraction of lifetime exposed and relative risk. The listed unit risk factor [2.4 E-3 $(\mu g/m^3)^{-1}$] is the arithmetic mean of the 8 derived unit risks. This unit risk may not be appropriate if the air concentration exceeds 4 $\mu g/m^3$ and should not be used under those circumstances.

Table II. Effective dose, upper-bound estimate of relative risk and unit risk of carcinogenicity due to human beryllium exposure via inhalation (US EPA, 1992).

Beryllium concentration in workplace ($\mu g/m^3$)	Fraction of lifetime	Effective dose ($\mu g/m^3$)	95% upper-bound estimate of relative risk	Unit risk/ ($\mu g/m^3$)
100	1.00	21.92	1.98	1.61E-3
			2.09	1.79E-3
	0.25	5.48	1.98	6.44E-3
			2.09	7.16E-3
1000	1.00	219.18	1.98	1.61E-4
			2.09	1.79E-4
	0.25	54.79	1.98	6.44E-4
			2.09	7.16E-4

Oral

A cancer potency factor (q_1*) was derived by fitting a linearized multistage model to the tumor incidence data presented in Schroeder and Mitchener (1975a). Surface area scaling was employed to transform animal cancer potency factors to human cancer potency factors. Assumed body weight values for humans and rats were 70 kg and 0.325 kg, respectively.

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BIS(2-CHLOROETHYL)ETHER

CAS No: 111-44-4

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	143.02
Boiling point	176-178.5°C
Melting point	-24.5°C
Vapor pressure	0.7 mm Hg @ 20°C
Air concentration conversion	1 ppm = 5.8 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 7.1 E-4 $(\mu g/m^3)^{-1}$
Slope Factor: 2.5 E+0 $(mg/kg\text{-}day)^{-1}$
[Calculated from a cancer potency factor derived by RCHAS/OEHHA (CDHS, 1988)]

III. CARCINOGENIC EFFECTS

Human Studies

There are no human carcinogenicity studies available for bis(2-chloroethyl)ether (BCEE).

Animal Studies

Two studies address the carcinogenicity of bis(2-chloroethyl)ether by the oral route of exposure. Innes *et al.* (1969) administered 100 mg/kg body weight bis(2-chloroethyl)ether by oral gavage to two F_1 generation strains of mice termed X (C57BL/6 × C3H/Anf) and Y (C57BL/6 × AKH) (18/sex/strain) from day 7 to 28 of life, without adjusting the initial dose to account for weight gain. After 28 days, BCEE was added to feed at a concentration of 300 ppm for 76 weeks. Surviving animals were sacrificed at 80 weeks. Ninety animals of each strain were included as controls. Tumor incidence in surviving animals is summarized in Table 1. A statistically significant increase in hepatomas ($p<0.05$) was noted in both males and females of strain X and in males of strain Y. No other tumor type showed significant increases in incidence.

Charles River CD rats (26/sex/group) were treated with 0, 25 or 50 mg/kg-day bis(2-chloroethyl)ether by gavage for 18 months by Weisburger *et al.* (1981). Animals were observed for 2 years. No carcinogenic effects were observed, although the authors report increased mortality among the high-dose females and reduction in mean weight among high-dose males and females.

Van Duuren *et al.* (1972) report on two experimental approaches to evaluate the carcinogenicity of bis(2-chloroethyl)ether; a subcutaneous injection study and an initiation study by dermal

application. ICR/Ha Swiss mice (30 females) were injected weekly with 1 mg BCEE for 685 days. No tumors remote from the injection site were observed. Two sarcomas were noted at the injection site (2/30) but were not found to be statistically different from controls (0/30) ($p>0.05$ by Fisher's Exact Test).

Van Duuren *et al.* (1972) also treated ICR/Ha Swiss mice (20 females/group) with a single dose of 1 mg BCEE applied to the skin followed by three applications/week of the tumor promoter phorbol myristate acetate (PMA) in acetone for life. Control groups included animals not treated with BCEE and animals treated with BCEE but without the promoter. Skin papillomas were noted among animals treated with both BCEE and PMA, but the incidence was not significantly higher than among control animals (3/20 treated, 2/20 controls; $p>0.05$ by Fisher's Exact Test). No tumors were observed among animals treated only with BCEE.

Theiss *et al.* (1977) injected A/St mice (20 males) intraperitoneally with 8, 20, or 40 mg/kg BCEE 3 times/week for 8 weeks. After 24 weeks all surviving mice were sacrificed and examined only for lung tumors. The incidence of tumors among treated animals was not found to be significantly higher than among controls.

Table 1. Incidence of tumors in rats treated with bis(2-chloroethyl)ether[*] (Innes *et al.*,1969).

		Tumor Incidence			
		Strain X		Strain Y	
Tumor Type/Treatment		female	male	female	male
hepatomas	treated	4/18[**]	14/16[**]	0/18	9/17[**]
	control	0/87	8/79	1/82	5/90
pulmonary tumors	treated	0/18	0/16	0/18	2/16
	control	3/83	5/79	3/92	10/90
lymphomas	treated	0/18	2/16	0/18	0/17
	control	4/87	5/79	4/82	1/90

[*] F_1 generation mice were administered 100 mg/kg body weight bis(2-chloroethyl)ether by oral gavage from day 7 to 28 of life and subsequently in feed at a concentration of 300 ppm for 76 weeks (calculated dose is 39 mg/kg-day). Surviving mice were sacrificed at 80 weeks.
[**] statistically significant increase in incidence ($p<0.001$ by Fisher's exact test)

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

In the absence of studies in humans useful in evaluating the carcinogenicity of bis(2-chloroethyl)ether, a single animal study (Innes *et al.*, 1969) has been identified as appropriate for the development of a cancer potency value. The most sensitive endpoint from this study is the development of hepatomas in treated male strain X rats. Other studies either do not show development of tumors (Weisburger, 1981) or experimental duration/dosing limited the interpretation of negative data (Van Duuren, 1972; Theiss, 1977).

Methodology

Lifetime average dose estimates from the Innes *et al.* study (1969) have been calculated to be 39 mg/kg-day bis(2-chloroethyl)ether (US EPA, 1980). A linearized multistage model polynomial was fit to the tumor incidence data (CDHS, 1985; Anderson, 1983). The upper 95% confidence bound on the cancer potency estimate is termed q_1^*. Using the data presented in Table 1, the following cancer potencies were derived from groups showing significant increases in hepatoma incidence:

animal group	q_1^* (mg/kg-day)$^{-1}$
Strain X - males	0.086
Strain X - females	0.013
Strain Y - males	0.031

The selection of the cancer potency value has been based on the q_1^* value from the most sensitive sex and strain in this case, 0.086 (mg/kg-day)$^{-1}$ in Strain X males derived from Innes *et al.*(1969). Calculation of the cancer potency in animals (q_{animal}) can be made from the following relationship, where T is the natural lifespan of the animal (104 weeks) and T_e is the experimental duration (80 weeks):

$$q_{animal} = q_1^* \times (T/T_e)^3$$

The resulting q_{animal} is 0.19 (mg/kg-day)$^{-1}$. Conversion to human cancer potency (q_{human}) is based on the following relationship, where bw_{animal} is the assumed body weight for the test species (0.03 kg - mice; US EPA, 1980) and bw_{human} is the assumed human body weight (70 kg):

$$q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$$

The estimate of q_{human} based on this relationship is 2.5 (mg/kg-day)$^{-1}$. A unit risk value based upon air concentrations was derived by OEHHA/ATES asssuming the human breathing rate of 20 m^3/day, 100% fractional absorption, and average human body weight of 70 kg. The calculated unit risk value is 7.1 E-4 ($\mu g/m^3$)$^{-1}$.

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BIS(CHLOROMETHYL)ETHER

CAS No: 542-88-1

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	114.96
Boiling point	106°C
Melting point	-41.5°C
Vapor pressure	30 mm Hg at 22°C
Air concentration conversion	1 ppm = 4.75 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.3 E-2 $(\mu g/m^3)^{-1}$
Slope Factor: 4.6 E+2 $(mg/kg\text{-}day)^{-1}$
[Calculated from potency value derived by RCHAS, cross-route extrapolation (CDHS, 1988)]

III. CARCINOGENIC EFFECTS

Human Studies

Increases in the incidence of lung cancer have been reported in a number of studies of workers exposed to both bis(chloromethyl)ether (BCME) and chloromethyl methyl ether (CMME). Some of these studies involve workers primarily exposed to CMME contaminated with 1-8 % BCME. Exposure to CMME, a known human carcinogen, is a confounding variable in these studies. However, there are several studies in which individuals were known to have been exposed to BCME, but exposure to CMME was not known to have occurred and appears unlikely.

Theiss *et al*. (1973) (reviewed by IARC, 1973) reported a retrospective study of a small group of BCME workers exposed between 1956 and 1962. Six cases of lung cancer were found in 18 men employed in a testing facility; 5 of the 6 men were smokers. Two additional lung cancer cases were found in a group of 50 production workers. Five of the 8 total cases were oat-cell carcinomas. Exposure periods were 6-9 years, and tumor latency was 8-16 years.

Sakabe (1973) reported on lung cancer cases occurring in 32 workers exposed to BCME in a Japanese dyestuff factory in the period 1955-1970. Five cases of lung cancer were reported compared to 0.024 expected cases ($p < 0.001$). One case was reported to be oat-cell carcinoma; the others were of mixed histological types. Duration of exposure to BCME ranged from 4 to 7 years; cancer mortality latency ranged from 8 to 14 years after initial exposure. It was noted that all the workers that developed lung cancer were also smokers, and that 4 of the 5 cases were also exposed to other industrial chemicals.

Lemen *et al*. (1976) conducted a retrospective cohort study of cancer incidence in a group of 115 white male anion-exchange resin manufacturing workers in San Mateo County, California. Worker tobacco smoking status was evaluated and used to adjust expected tumor incidence rates. Five cases of lung cancer were observed compared to 0.54 cases expected ($p < 0.01$), representing a nine-fold increased lung cancer risk. The histological type of lung cancer primarily observed was small cell-undifferentiated; exposure ranged from 7.6 to 14 years (mean of 10 years). The mean induction-latency period was 15 years. No quantitative worker exposure evaluation was performed.

The studies described above demonstrated a significant increase in lung cancer incidence, predominantly small-cell-undifferentiated carcinoma. This histologic type is not the one generally associated with smoking (squamous cell carcinoma).

Animal Studies

Male Sprague-Dawley rats and golden Syrian hamsters (50/exposure group) received 1, 3, 10 or 30 exposures (6 hours/exposure) to 1 ppm BCME by inhalation (Drew *et al*., 1975). After exposure, the animals were exposed for the remainder of their lifetime. Median survival time for hamsters receiving 0, 1, 3, 10 or 30 exposures was 675, 620, 471, 137 and 42 days, respectively. Median survival time for exposed rats was 467, 457, 168, 21 and 23 days, respectively. One rat in the 3 exposure group developed a squamous-cell carcinoma of the skin; additionally, one hamster in the 1 exposure group developed an undifferentiated nasal tumor. These tumor incidences were not statistically significant. However, the study treatment durations were short, and survival of the treated animals was poor.

Kuschner *et al*. (1975) exposed male Sprague-Dawley rats and golden Syrian hamsters to BCME by inhalation. Groups of 100 hamsters and 70 rats were exposed to 0.1 ppm BCME 6 hours/day, 5 days/week. Control group sizes were not stated. Exposure was generally for the life of the animals. After 80 exposures, 57/70 rats were still alive; 20 rats were then removed from the exposure schedule and observed for the remaining life of the animals. Mortality at 60 weeks was approximately 90% for rats (both animals exposed for their entire lifetime and animals receiving 80 exposures) and hamsters; corresponding control mortality at 60 weeks was approximately 40% and 15% for rats and hamsters, respectively. Two rats in the group receiving 80 exposures developed tumors; the tumor types were a nasal esthesioneuroepitheloma and a keratinizing squamous cell carcinoma of the lung. Additionally, one hamster developed an undifferentiated carcinoma of the lung. No corresponding tumors were reported in control rats or hamsters. Additional groups of rats were given 0, 10, 20, 40, 60, 80 or 100 6-hour exposures to 0.1 ppm BCME (group sizes 240, 50, 50, 20, 20, 30, and 30, respectively), then observed for the life of the animals. Mortality of the exposed animals in all exposure groups was equivalent to that of controls. Nasal and lung tumors were noted in the exposed animals. Nasal tumor types included esthesioneuroepithelomas, unclassified malignant olfactory tumors, squamous cell carcinomas involving the turbinates and gingiva, poorly differentiated epithelial tumors and adenocarcinomas of the nasal cavity. Lung tumors included squamous cell carcinomas and adenocarcinomas. Tumor incidence data for combined respiratory tract tumors is listed in Table 1.

Table 1. Bis(chloromethyl)ether-induced respiratory tract tumors in male Sprague-Dawley rats (Kuschner *et al*., 1975)

Number of exposures (6 hours, 0.1 ppm)	Human equivalent[1] $(mg/kg/day)^{-1}$	Tumor incidence[2]
0	0	0/240
10	0.00027	11/41
20	0.000541	3/46
40	0.00105	4/18
60	0.00184	4/18
80	0.00347	15/34
100	0.00373	12/20

1. Calculated by US EPA (1991)
2. Incidence of respiratory tract cancers in animals surviving beyond 210 days.

Male Sprague-Dawley rats (Spartan substrain) (120/group) and Ha/ICR mice (144-157/group) were exposed to 0, 1, 10 or 100 ppb BCME by inhalation for 6 hours/day, 5 days/week for 6 months (Leong *et al*., 1981). The animals were then observed for the duration of their lifespan. No significant increases in mortality were associated with BCME exposure, except for the 100 ppb exposure group; all animals in this group were dead by 19 months. Significant treatment-related increases in the incidence of respiratory tract tumors were noted. Tumor types included nasal esthesioneuroepithelomas and carcinomas, and pulmonary adenomas. Tumor incidence data is listed in Table 2.

Table 2. Bis(chloromethyl)ether-induced nasal tumors in male Sprague-Dawley rats (Leong *et al*., 1981)

Concentration[1] (ppb)	Tumor Incidence[2]
0	0/112
1	0/113
10	0/111
100	97/112

1. Animals were exposed to 0, 1, 10, 100 ppb BCME for 6 hours/day, 5 days/week for 6 months.
2. Incidence of nasal tumors as reported by CDHS (1988).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Cancer potency factors for BCME were derived from male Sprague-Dawley rat respiratory tract tumor data (Kuschner *et al*., 1975; Leong *et al*., 1981). Cancer potency values are based on the most sensitive site, species and study demonstrating carcinogenicity of a particular chemical, unless other evidence indicates that the value derived from that data set is not appropriate (CDHS, 1985). The Kuschner *et al.* (1975) study used relatively high exposure levels of BCME. The exposure levels used in the Leong *et al*. (1981) study were lower, and the dose-response exhibited is highly non-linear. Therefore, a cancer potency estimated from the Leong *et al*. (1981) data set may be more representative of low-dose rate potency. For low dose exposures to BCME (below 1 ppb), the potency value was calculated from dose-response data published by Leong *et al*. (1981); for periodic high dose exposures (at or above 1 ppb BCME), the potency was derived from the study by Kuschner *et al*. (1975) (CDHS, 1988).

Methodology

Cancer potency factors (q_1^*) were derived by fitting a linearized multistage model (CDHS, 1985) to the dose-response data for male Sprague-Dawley rat respiratory tract tumors (Kuschner *et al.*, 1975) and nasal tumors (Leong *et al*., 1981). Absorbed doses were calculated assuming complete absorption of inhaled BCME, using an inspiration rate of 0.29 m^3/day for Sprague-Dawley rats. The dose from a continuous exposure to 1 ppb BCME (4.7 µg/m^3) would therefore be 1.36 µg/day, or 2.6 µg/kg-day. The cancer potency factors (q_1^*) derived from the Leong *et al*. (1981) and Kuschner (1975) data sets were 8.9 $(mg/kg/day)^{-1}$ and 47 $(mg/kg/day)^{-1}$, respectively. Surface area scaling was employed to transform animal cancer potency factors to human cancer potency factors, using the relationship ($q_{human} = q_{animal} * (bw_h / bw_a)^{1/3}$), where q_{human} is the human potency, q_{animal} is the animal potency, and bw_h and bw_a are the human and animal body weights, respectively. Body weight values used for humans and Sprague-Dawley rats were 70 kg and 0.52 kg, respectively. The human cancer potency factors (q_1^*) derived from the Leong *et al*. (1981) and Kuschner (1975) data sets were 45.6 $(mg/kg/day)^{-1}$ and 240 $(mg/kg/day)^{-1}$, respectively. The unit risk factor was derived by OEHHA/ATES from the low dose exposure cancer potency value using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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CHLORINATED PARAFFINS (Average chain length C12, 60% chlorine by weight)

CAS No: 108171-26-2

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB (1994) except where noted)

Molecular weight	411 (average) [NTP, 1986]
Boiling point	not available
Melting point	not available
Vapor pressure	not available
Air concentration conversion	1 ppm = 17 mg/m^3 (approximate)

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.5 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 8.9 E-2 $(mg/kg\text{-}day)^{-1}$
[NTP (1986) female mouse liver tumor data, contained in Gold *et* al. database (1990), expedited Proposition 65 methodology (OEHHA, 1992), cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of chlorinated paraffins are known to exist.

Animal Studies

Male and female $B6C3F_1$ mice and Fischer 344N rats (50/sex/group) were treated by gavage with a commercial-grade chlorinated paraffin product dissolved in corn oil 5 days/week; treatment duration was 103 and 104 weeks for mice and rats, respectively (NTP, 1986). Exposure levels were 0, 125 and 250 mg/kg body weight for mice, and 0, 312 and 625 mg/kg for rats. Significant increases in the incidence of liver tumors were noted in male and female mice; the incidence of alveolar and bronchiolar carcinoma was significantly increased in male mice, as was the combined incidence of thyroid follicular-cell adenomas and carcinomas in female mice. Tumor incidences in mice are listed in Table 1.

Significant increases in liver tumor incidence were noted in male and female rats. Significant increases were also noted in the incidence of leukemia in male rats, and in the incidence of thyroid follicular-cell tumors in female rats. Tumor incidences in rats are listed in Table 2.

Table 1. Tumors induced in $B6C3F_1$ mice by gavage administration of chlorinated paraffins (NTP, 1986)

Dose (mg/kg bw)	Hepatocellular adenomas	Hepatocellular adenomas and carcinomas	Alveolar/bronchiolar carcinomas	Thyroid follicular-cell tumors
Males				
0	11/50	20/50	0/50	
125	20/50	34/50	3/50	
250	29/50	38/50	6/50	
Females				
0	0/50	3/50		8/50
125	18/50	22/50		12/49
250	22/50	28/50		13/49

Table 2. Tumors induced in Fischer 344 rats by gavage administration of chlorinated paraffins (NTP, 1986)

Dose (mg/kg bw)	Hepatocellular carcinomas	Hepatocellular adenomas and carcinomas	Mononuclear cell leukemia	Thyroid follicular-cell tumors
Males				
0	0/50	0/50	7/50	
312	10/50	13/50	12/50	
625	16/48	16/50	14/50	
Females				
0	0/50	0/50		0/50
312	4/50	5/50		6/50
625	7/50	7/50		6/50

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Results of the NTP (1986) gavage study of chlorinated paraffins in male and female $B6C3F_1$ mice and F344 rats are listed in Gold et al. (1990). Benign and malignant liver tumors were observed in both sexes and species; significant elevations in tumor incidences at other sites were also observed. Estimates of cancer potency are similar for male and female mice and male rats. Cancer potency is based on dose-response data for benign and malignant liver tumors in female mice (see Table 1) (OEHHA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

California Environmental Protection Agency (Cal/EPA) 1992. Expedited Cancer Potency Values and Proposed Regulatory Levels for Certain Proposition 65 Carcinogens. Office of Environmental Health Hazard Assessment, Reproductive and Cancer Hazard Assessment Section, Berkeley, CA.

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4-CHLORO-*o*-PHENYLENEDIAMINE

CAS No: 95-83-0

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	142.60
Boiling point	not available
Melting point	76 °C (NCI, 1978)
Vapor pressure	not available
Air concentration conversion	1 ppm = 5.83 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 4.6 E-6 $(\mu g/m^3)^{-1}$
Slope Factor: 1.6 E-2 $(mg/kg\text{-}day)^{-1}$
[Male rat urinary bladder tumor data (NCI, 1978), contained in Gold *et al.* (1990), expedited Proposition 65 methodology (Cal/EPA, 1992), cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of 4-chlor*o*-o-phenylenediamine in humans are known to exist.

Animal Studies

Male and female Fischer 344 (F344) rats and B6C3F_1 mice were fed diets containing 4-chloro-*o*-phenylenediamine (NCI, 1978). Dietary 4-chloro-*o*-phenylenediamine concentrations and treatment durations for rats and mice are listed in Table 1. Treatment group sizes were 50 animals/sex/species/group, except for low-dose male rats, where a group size of 49 was used.

At study termination, 84, 84 and 70% of male mice, and 72, 88 and 78% of female mice in the control, low-dose and high-dose groups, respectively, were still alive. Survival in treated rats was somewhat lower; 64, 80 and 56% of male rats and 72, 84 and 54% of female rats in the control, low-dose and high-dose groups, respectively, were still alive at study termination. Significantly increased treatment-related liver tumor (hepatocellular adenomas, carcinomas) incidences were noted in both male and female mice. These data are listed in Table 2. A significant dose-related trend was also noted in the increased incidence of urinary bladder carcinomas in male (transitional cell papillomas, carcinomas) and female (papillary or transitional cell carcinomas) rats (Table 2). Increases in the incidence of forestomach tumors also occurred in both male and female rats. The forestomach tumor increases were not statistically significant; however, these tumors are rare in F344 rats.

Table 1. Study design summary for NCI (1978) carcinogenicity bioassay of 4-chloro-*o*-phenylenediamine in Fischer 344 rats and B6C3F$_1$ mice.

Sex/species	Treatment group	4-chloro-*o*-phenylenediamine concentration (mg/kg diet)	Observation period		Time-weighted average concentration (mg/kg diet)
			Treated (weeks)	Untreated (weeks)	
Male rats	control	0		105	
	low-dose	5000	78		
				27	
	high-dose	10000	78		
				28	
Female rats	control	0		106	
	low-dose	5000	78		
				28	
	high-dose	10000	78		
				28	
Male mice	control	0		97	0
	low-dose	10000	33		7000
		5000	45		
		0		17	
	high-dose	20000	33		14000
		10000	45		
		0		18	
Female mice	control	0		97	0
	low-dose	10000	33		7000
		5000	45		
		0		18	
	high-dose	20000	33		14000
		10000	45		
		0		18	

Table 2. Tumor induction in F344 rats and B6C3F$_1$ mice fed diet containing 4-chloro-*o*-phenylenediamine (NCI, 1978)

Sex/species	Dose group	Average dose[1] (mg/kg-day)	Tumor type	Tumor incidence[2]
Male rats	control	0	urinary bladder tumors	0/50
	low-dose	149		15/49
	high-dose	294		25/50
Female rats	control	0	urinary bladder tumors	0/50
	low-dose	184		5/50
	high-dose	368		22/50
Male mice	control	0	liver tumors	15/50
	low-dose	701		28/50
	high-dose	1390		34/50
Female mice	control	0	liver tumors	0/50
	low-dose	752		11/50
	high-dose	1500		10/50

1. Doses as reported by Gold *et al.* (1984).
2. Tumor incidences as reported by Gold *et al.* (1984).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Gold *et al.* (1984) list results of the NCI (1978) feeding study in male and female B6C3F$_1$ mice and F344 rats. Benign and malignant neoplasms of the liver were elevated in treated male and female mice. Forestomach tumors were also observed in treated rats; these tumors are relatively uncommon in this strain. In addition, substantial increases in the incidences of urinary bladder cancers were seen in rats of both sexes. Dose-response data are given in Table 2. Rats appear to be more sensitive than mice. Quantitative analysis of dose-response data for urinary bladder tumors indicate that male and female rats have nearly the same sensitivity. The upper confidence bound on potency for data on male rats is slightly higher, and this is the value used as a cancer potency for 4-chloro-*o*-phenylenediamine (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

California Environmental Protection Agency (Cal/EPA) 1992. Expedited Cancer Potency Values and Proposed Regulatory Levels for Certain Proposition 65 Carcinogens. Office of Environmental Health Hazard Assessment, Reproductive and Cancer Hazard Assessment Section, Berkeley, CA.

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p-CHLORO-*o*-TOLUIDINE

CAS No: 95-69-2

p-CHLORO-*o*-TOLUIDINE HYDROCHLORIDE

CAS No: 3165-93-3

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

_p_-Chloro-_o_-toluidine

Molecular weight	141.61
Boiling point	241 °C
Melting point	30 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 5.79 mg/m^3

_p_-Chloro-_o_-toluidine hydrochloride

Molecular weight	178.07
Boiling point	not available
Melting point	not available
Vapor pressure	not available
Air concentration conversion	1 ppm = 7.3 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 7.7 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 2.7 E-1 $(mg/kg\text{-}day)^{-1}$
[Male and female mouse hemangioma and hemangiosarcoma tumor data (Weisburger *et* al., 1978; NCI, 1979), contained in Gold *et* al. database (1984), expedited Proposition 65 methodology (Cal/EPA, 1992), cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

IARC (1990) reviewed studies by Currie (1933) and Uebelin and Pletscher (1954) which investigated bladder tumor incidence in small groups of male workers exposed to *p*-chlor*o*-*o*-toluidine; one case of bladder carcinoma was discovered (Currie, 1933).

A cohort study by Ott and Langner (1983) investigated 342 male workers involved in the manufacture of organic dyes in the US between 1914 and 1958. One plant area involved 117 workers with potential exposure to *p*-chlor*o*-*o*-toluidine and other raw materials and intermediates, including *ortho*-toluidine. Followup of this subcohort from 1940 to 1975

indicated that a nonsignificant excess of total cancer deaths occurred (12 observed, 8 expected) and no bladder cancer was observed.

Two studies were conducted on a cohort of 355 male workers in *p*-chloro*-o*-toluidine manufacturing plants in the Federal Republic of Germany (FRG) who had been followed up for mortality from 1929 to 1982. No deaths due to bladder cancer were found in the first study (Stasik *et al*., 1985). The second study examined a subcohort of 116 workers exposed prior to 1970 (the implementation date of improved exposure controls) with presumed high *p*-chloro*-o*-toluidine exposure levels. Excluding 2 cases of urinary bladder carcinomas in the current work force, 6 cases of bladder carcinoma were found between January 1983 and June 1986 in hospital and other institution records. No cancer registry data was available for the area of the FRG where the plant was located; cancer registration rates for a different area of the FRG was therefore used as a basis of comparison. The expected number of tumors was 0.11 based on sex- and age-specific cancer rates. Two patients had hemorrhagic cystitis thought to be due to massive exposure to *p*-chloro*-o*-toluidine. Cigarette smoking was discounted as a confounding variable after reviewing patient smoking histories (3 patients were nonsmokers). Quantitative exposure data was unavailable, but the predominant chemical exposure was to *p*-chloro*-o*-toluidine; however, exposure to other amines could have occurred.

Animal Studies

Male and female random-bred CD-1 albino mice (derived from HaM/ICR mice) and male Charles River CD Sprague-Dawley-derived rats (25/sex/group) were fed diets containing *p*-chloro*-o*-toluidine hydrochloride (97-99% pure) as part of a larger carcinogenicity study of several compounds (Weisburger *et al*., 1978). Mouse exposure levels were 0, 750 or 1500 mg/kg diet and 0, 2000 or 4000 mg/kg diet for males and females, respectively; the mice were fed treated diet for 18 months, followed by an additional 3 month observation period. Rats were fed diet containing 2000 or 4000 mg/kg diet *p*-chloro*-o*-toluidine for 3 months; the doses were then reduced to 500 and 1000 mg/kg diet for 15 months. An untreated control group (25 males) was included. All rats were killed after 24 months. Tumor incidence differences between control and exposed rat groups were not statistically significant. Hemangiomas and hemangiosarcomas were observed in male and female mice; tumor incidence data is listed in Table 1. These tumor types were found in 5/99 male and 9/102 female pooled controls from the larger carcinogenicity study, but were not present in the simultaneous controls.

Diets containing *p*-chloro*-o*-toluidine hydrochloride (99% pure) were fed to groups of male and female $B6C3F_1$ mice and Fischer 344 (F344) rats (50 animals/sex/species/treatment group) (NCI, 1979). Exposure levels for mice were 3750 or 15000 and 1250 or 5000 mg/kg diet for males and females, respectively. Exposure levels for rats were 1250 or 5000 mg/kg diet. Untreated control groups (20 animals/sex/species) were included. Exposed animals were fed treated diet for the duration of the study. All surviving mice were killed at 99 weeks; however, all high-dose females had died by 92 weeks. All surviving rats were killed at 107 weeks.

Exposure to *p*-chloro-*o*-toluidine did not affect mortality of either male or female rats; a dose-related increase in mortality was noted for both male and female mice (NCI, 1979). However,

sufficient numbers of mice of each sex were at risk for tumor development for determination of tumor incidence significance. The percentage of mice surviving to study week 52 was at least 95% for all sexes and treatment groups. No significant tumor incidence increase was observed in male or female F344 rats as a result of *p*-chloro-*o*-toluidine exposure. Significant treatment-related increases ($p < 0.001$) were observed in the incidence of both hemangiosarcomas and hemangiomas and hemangiosarcomas combined in both male and female mice. Tumor incidence data is listed in Table 1.

Table 1: Incidence of vascular tumors (hemangiomas and hemangiosarcomas) in male and female mice treated with *p*-chloro*-o*-toluidine hydrochloride by dietary administration

Study	Sex/Strain	Dietary concentration (mg/kg diet)	Average Dose[1] (mg/kg-day)	Tumor Incidence
Weisburger et al. (1978)[2]	male CD-1	0 750 1500	0 90 180	0/14 12/20 13/20
Weisburger et al. (1978)[3]	female CD-1	0 2000	0 260	0/15 18/19
NCI (1979)[2]	male $B6C3F_1$	0 3750 15000	0 450 1800	0/20 6/50 41/50
NCI (1979)[3]	female $B6C3F_1$	0 1250	0 162	1/20 43/50

1. Doses as reported by Gold et al. (1984).

2. Decreased survival according to Gold et al.; a time-to-tumor analysis was performed using TOX_RISK (Crump et al., 1991; Cal/EPA, 1992).

3. Analysis of the data set using the computer program TOX_RISK (Crump et al., 1991) indicated that inclusion of the high dose group resulted in a *p*-value of ≥ 0.05 based on the chi-square goodness-of-fit test, indicating non-linearity. Following procedures described by US EPA (Anderson *et al*., 1983), the high dose group was excluded from the analysis to correct for the poor fit (Cal/EPA, 1992).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

On the basis of positive bioassay results, the hydrochloride salt of *p*-chloro*-o*-toluidine was classified as a compound with sufficient evidence of carcinogenicity in animals by IARC (1987).

The results of feeding studies on by NCI (1979) using male and female $B6C3F_1$ mice and Fischer 344 rats and by Weisburger *et al.* (1978) using male and female CD-1 HaM/ICR mice and male Charles River CD rats are reported in Gold et al. (1984). In contrast to rats, mice are sensitive to *p*-chlor*o*-*o*-toluidine hydrochloride-induced carcinogenicity. Vascular tumors (hemangiomas and hemangiosarcomas) were induced in treated mice of both strains and sexes tested.

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. The cancer potency for *p*-chlor*o*-*o*-toluidine is based on the bioassay results for the hydrochloride, adjusted for differences in molecular weight. An overall cancer potency was estimated by taking the geometric mean of the 4 values derived from dose-response data for vascular tumors from each of the mouse sex and strains tested (male and female CD-1 and $B6C3F_1$ mice) (Weisburger *et* al., 1978; NCI, 1979; see Table 1). Male $B6C3F_1$ mouse survival in the NCI (1979) study was poor; a cancer potency for that sex and strain was therefore derived using a time-to-tumor analysis (Crump et al., 1991; Cal/EPA, 1992). A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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CREOSOTE (COAL TAR-DERIVED)

CAS No: 8001-58-9

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	complex mixture
Boiling point	194 - 400ºC
Melting point	not available
Vapor pressure	not available
Air concentration conversion	not available

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: Can be calculated using PEF factors contained in the benzo[a]pyrene Toxic Air Contaminant (TAC) document (OEHHA, 1993).

Slope Factor: Can be calculated using PEF factors contained in the benzo[a]pyrene TAC document (OEHHA, 1993).

III. CARCINOGENIC EFFECTS

Human Studies

Henry (1947) reviewed 3753 cases of cutaneous epitheliomata (epitheliomatous ulceration or cancer of the skin) reported to the British Medical Inspector of Factories from 1920 to 1945. Thirty five cases (12 of the scrotum) had creosote exposure. Henry (1946) also reported that the crude mortality rate for scrotal cancer during 1911-1938 for British brickmakers exposed to creosote oil was 29 per million men based on 9 verified cases as compared to a national average of 4.2 per million and rates of 1 per million or less for groups not exposed to suspected skin carcinogens.

A cohort study reported on 123 Swedish workers who treated wood with creosote and were exposed to both creosote and arsenic between 1950 and 1980 (Axelson and Kling, 1983; reviewed in IARC, 1985). Eight workers died of cancer compared to 6 expected. Three cancer deaths (leukemia, pancreas and stomach) were observed compared to 0.8 expected in a subgroup of 21 workers exposed only to creosote for five or more years.

A case-referent study of Swedish workers examined potential relationships between past occupational and radiation exposure and multiple myeloma (Flodin *et al*., 1987). Exposure assessment employed a mailed questionnaire that asked questions about occupational (including coal tar creosote) and radiation exposure. Data analysis using the Miettinen confounder score technique indicated that an increased prevalence of multiple myeloma was associated with occupational exposure to coal tar creosote (crude rate ratio = 6.0, p = 0.001). The rate ratio point estimate for creosote exposure increased to 9.0 after age stratification. The power of this study

was limited by differences between the case group and the referent group in the number of smokers and gender composition.

Creosote contains many of the same compounds present in other polycyclic aromatic hydrocarbon (PAH) mixtures (roofing tar pitch, coke oven emissions) known to be human carcinogens (US EPA, 1986; ATSDR, 1990).

Animal Studies

Female C57BL mice (10 animals/group) were exposed to blended creosote oil (a mixture of creosote, anthracene oils and naphthalene recovery residue oil) in toluene. One drop (8.7 - 9 µl) of a 20% or 80% solution was applied to the skin three times/week for the animals' lifetimes or until tumors developed (21 - 44 weeks and 18 - 35 weeks for the 20% and 80% solution exposure groups, respectively). All treated mice developed skin papillomas and 7 mice in each group developed epidermoid carcinomas, some of which metastasized to pulmonary or regional lymph nodes. None of the vehicle control animals developed skin tumors (Poel and Kammer, 1957).

Female Swiss mice (30/group) were treated twice weekly with one drop of a 2% solution of creosote in acetone applied dermally for 70 weeks. Skin tumors (including 16 carcinomas) were reported in 23 of 26 surviving mice. The average tumor latency period was 50 weeks. No vehicle control group was included; however, no animals in a control group of 50 mice receiving a single application of 1% 7,12-dimethylbenz[*a*]anthracene in mineral oil developed tumors after 80 weeks (Lijinsky *et al*., 1957).

Undiluted creosote applied topically twice weekly (25 µl) to 30 random-bred female mice for 28 weeks induced an average of 5.4 papillomas per animal; 82% of the mice had carcinomas. The average time to tumor for papillomas and carcinomas was 20 and 26 weeks, respectively. No vehicle control group was included in the study (Boutwell and Bosch, 1958). In a similar study, a group of 24 albino mice treated dermally with 25 µl creosote twice weekly for 5 months and housed in stainless steel cages exhibited 139 lung adenomas (5.8 tumors/mouse) after 8 months. A group of 29 mice born and housed in creosote-treated wood cages treated dermally with 25 µl creosote for 5 months demonstrated 315 lung adenomas (10.8 tumors/mouse) after 8 months. A control group (19 mice) housed in stainless steel cages demonstrated 9 lung adenomas (0.5 tumors/mouse) after 8 months (Roe *et al*., 1958).

V. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Creosote has been demonstrated to cause skin and lung tumors in mice after dermal exposure, and is predominantly composed of PAH; similar PAH-containing coal tar products (roofing tar pitch, coke oven emissions) have been shown to be human carcinogens (US EPA, 1986; ATSDR, 1990). Creosote has been given B1 and 2A classifications (probable human carcinogen) by US EPA (1987) and IARC (1985), respectively. No creosote carcinogenicity bioassay study suitable for quantitative risk assessment exists. However, a cancer unit risk factor for the PAH

benzo[*a*]pyrene (BaP) derived from an inhalation exposure study (Thyssen *et al*., 1981) has been developed, along with Potency Equivalency Factors (PEFs) for several related PAHs. (OEHHA, 1993).

Thyssen *et al*. (1981) exposed male Syrian golden hamsters (24/group) by inhalation to 0. 2.2, 9.5 or 46.5 mg BaP/m^3 in a sodium chloride aerosol (greater than 99% of the particle diameters were between 0.2 and 0.5 µm). The hamsters were exposed to BaP daily for 4.5 hours/day for the first 10 weeks of exposure; subsequent exposure was daily for 3 hours/day. Total treatment duration was 95 weeks. Animals dying in the first year of the study were replaced. The effective number of animals in the control, 2.2, 9.5 and 46.5 mg/m^3 exposure groups were 27, 27, 26 and 25, respectively. Survival time for the 46.5 mg/m^3 exposure group was significantly reduced (60 weeks) when compared to controls (96 weeks). Survival times for the other exposure groups were similar to controls. Respiratory tract (including nasal cavity, larynx and trachea) tumor incidence was significantly increased in a dose-dependent manner in the 9.5 and 46.5 mg/m^3 exposure groups (34.6% and 52%, respectively, compared to controls); those exposure groups also demonstrated an increase in upper digestive tract (including pharynx, esophagus and forestomach) tumor incidence (27% and 56%, respectively). This study was selected as the basis of a cancer potency factor for exposure to BaP by inhalation because it used the most sensitive species and sex demonstrating a dose response and using the most relevant exposure route.

Methodology

A linearized multistage model (GLOBAL86) (Howe and van Landingham, 1986) was fitted to the Syrian golden hamster respiratory tract tumor incidence data of Thyssen *et al*. (1981) and used to calculate a cancer potency factor. Data from the highest exposure group (46.5 mg/m^3) was not used due to the shortened lifespan of the hamsters in this group. Administered dose for the 2.2 and 9.5 mg/m^3 exposure groups based on an inspiration rate of 0.063 m^3/day and a body weight of 0.1 kg was 0.152 and 0.655 mg/kg/day, respectively. Surface area scaling was then used to extrapolate a human cancer potency factor and an inhalation unit risk factor (using assumptions of 70 kg body weight and 20 m^3/day inspiration rate). Creosote is approximately 91% PAH, nitro-PAH or hydroxy-PAH (Wright *et al*., 1985); a unit risk for creosote can be calculated using the unit risk value for BaP and the PEFs for related PAHs (OEHHA, 1993).

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p-CRESIDINE

CAS No: 120-71-8

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	137.20
Boiling point	235 °C
Melting point	51.5 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 5.611 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 4.3 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 1.5 E-1 $(mg/kg\text{-}day)^{-1}$
[Female mouse urinary bladder tumor data (NCI, 1979), contained in Gold *et* al. (1984), expedited Proposition 65 methodology, with cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of *p*-cresidine in humans are known to exist.

Animal Studies

Male and female Fischer 344 (F344) rats and B6C3F$_1$ mice (50 animals/sex/species/group) were fed diets containing *p*-cresidine (NCI, 1979). The study design is outlined in Table 1. Dose levels for male and female mice were reduced after 21 weeks; the study report did not describe the rationale for the dose reduction.

Mortality in mice was dose-related and associated with the development of bladder tumors; mortality in rats was also dose-related and was related to development of urinary bladder and nasal cavity tumors. Survival percentages after 75 weeks of treatment are listed in Table 2. Significant incidence increases were seen for urinary bladder tumors in male and female rats (squamous-cell or transitional-cell carcinomas) and mice (transitional-cell carcinomas), for liver tumors in female mice (hepatocellular adenomas or carcinomas) and male rats (neoplastic liver nodules, hepatocellular carcinomas or cholangiocarcinomas), and for nasal cavity tumors (primarily nasal cavity tumors) in male and female rats. These data are listed in Table 2. Nonsignificant increases in nasal cavity tumors were also observed in male and female mice.

Table 1. Study design summary for NCI (1979) carcinogenicity bioassay of *p*-cresidine in Fischer 344 rats and $B6C3F_1$ mice.

Sex/species	Treatment group	*p*-cresidine dietary concentration (mg/kg diet)	Observation period	
			Treated (weeks)	Untreated (weeks)
Male rats	control	0		106
	low-dose	5000	104	1
	high-dose	10000	104	1
Female rats	control	0		106
	low-dose	5000	104	2
	high-dose	10000	104	2
Male mice	control	0		97
	low-dose	5000	21	
		1500	83	
		0		2
	high-dose	10000	21	
		3000	71[a]	
Female mice	control	0		97
	low-dose	5000	21	
		1500	83	
		0		2
	high-dose	10000	21	
		3000	83	
		0		2

a. All animals in this group were dead by the end of week 92.

Table 2. Mortality and tumor incidences associated with dietary exposure of Fischer 344 rats and $B6C3F_1$ mice to *p*-cresidine (NCI, 1979)

Sex/species	Treatment group	Average Dose[1] (mg/kg-day)	Survival after 75 weeks (%)	Tumor type	Tumor incidence[2]
male mice	controls	0	98	urinary bladder tumors	0/50
	low-dose	260	50		40/50
	high-dose	552	10		31/50
female mice	controls	0	90	urinary bladder tumors	0/50
	low-dose	281	78		42/50
	high-dose	563	28		45/50
	controls			liver tumors	0/50
	low-dose				14/50
	high-dose				6/50
male rats	controls	0	94	urinary bladder tumors	0/50
	low-dose	198	96		30/50
	high-dose	396	62		44/50
	controls			liver tumors	0/50
	low-dose				13/50
	high-dose				2/50
	controls			nasal cavity tumors	0/50
	low-dose				2/50
	high-dose				23/50
female rats	controls	0	96	urinary bladder tumors	0/50
	low-dose	245	98		31/50
	high-dose	491	76		43/50
	controls			nasal cavity tumors	0/50
	low-dose				0/50
	high-dose				11/50

1. Doses as reported by Gold *et al*. (1984).
2. Tumor incidences as reported by Gold *et al*. (1984)

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Results of the NCI (1979) feeding study in male and female $B6C3F_1$ mice and Fischer 344 rats are listed in Gold et al. (1984). Urinary bladder tumors as well as tumors at other sites were observed in both sexes of mice and rats. The most sensitive site appears to be the urinary bladder. Both sexes of both species show similar sensitivities at this site. The potency derived from dose-response data on female mice (benign and malignant urinary bladder tumors) is slightly greater than those for the other groups and is taken as the best estimate here (see Table 2).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. Because female mouse survival was poor, the potency was derived using a time-to-tumor analysis (Crump et al., 1991; Cal/EPA, 1992). A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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CUPFERRON (N-hydroxy-N-nitroso-benzenamine, ammonium salt)

CAS No: 135-20-6

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	155.16
Boiling point	not available
Melting point	163-164 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 6.346 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 6.3 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 2.2 E-1 $(mg/kg\text{-}day)^{-1}$
[Male rat hemangiosarcoma data (NCI, 1978), contained in Gold *et* al. database (1984), expedited Proposition 65 methodology (Cal/EPA, 1992), cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of cupferron in humans are known to exist.

Animal Studies

Male and female Fischer 344 (F344) rats and $B6C3F_1$ mice were exposed to diets containing cupferron (NCI, 1978). A summary of the experimental design is outlined in Table 1. Treatment periods were followed by an observation period during which animals were fed control diet. Male and female mouse dose levels were reduced after 35 weeks. Group sizes were 50 animals/sex/species/group except for the high-dose male mouse group, which consisted of 49 animals.

Cupferron induced significantly increased incidences of forestomach squamous-cell carcinomas, hepatocellular neoplastic nodules and carcinomas in male and female rats, hemangiosarcomas in male and female rats and mice, auditory sebaceous gland tumors in female mice and rats, hepatocellular carcinomas in female mice and Harderian gland adenomas in male and female mice. Hemangiosarcoma incidence data is listed in Table 2.

Table 1. Experimental design for carcinogenicity bioassay of cupferron using male and female Fischer 344 (F344) rats and B6C3F$_1$ mice (NCI, 1978)

Sex/species	Group	Cupferron concentration (%)	Experiment duration (weeks)		Time-weighted average concentration[1]
			treatment period	observation period	
male rats	control	0	0	110	
	low dose	0.15	78	26	
	high dose	0.3	78	19	
female rats	control	0	0	110	
	low dose	0.15	78	28	
	high dose	0.3	78	28	
male, female mice	control	0		98	0
	low dose	0.3	35		0.2
		0.1	43	18	
	high dose	0.6	35		0.4
		0.2	43	17	

1. Time-weighted concentration $= \frac{\sum (\text{concentration} \times \text{weeks received})}{\sum (\text{weeks receiving chemical})}$

Table 2. Cupferron-induced hemangiosarcoma incidence in male and female F344 rats and B6C3F$_1$ mice (NCI, 1978)

Sex/species	Dose group	Average dose[1] (mg/kg-day)	Tumor incidence[2]
Male rat	control	0	0/50
	low dose	45	38/50
	high dose	96.5	35/49
Female rat	control	0	0/50
	low dose	55.2	28/50
	high dose	110	37/50
Male mouse	control	0	1/50
	low dose	185	3/50
	high dose	374	7/50
Female mouse	control	0	1/50
	low dose	200	5/50
	high dose	405	6/50

1. Doses as reported by Gold *et al*. (1984).
2. Tumor incidences as reported by Gold *et al*. (1984)

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Results of the NCI (1978) feeding study in male and female $B6C3F_1$ mice and Fischer 344 rats are listed in Gold *et al*. (1984). Benign and malignant vascular tumors as well as tumors at other sites were observed in mice and rats of both sexes treated with cupferron. Cancer potency is based on the data for vascular tumors in the male rat (see Table 2) because the rat is the more sensitive of the species tested, and the male appears to be slightly more sensitive than the female (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. Analysis of the data set using the computer program TOX_RISK (Crump et al., 1991) indicated that inclusion of the high dose group resulted in a p-value of ≥ 0.05 based on the chi-square goodness-of-fit test, indicating non-linearity. Following procedures described by US EPA (Anderson *et al*., 1983), the high dose group was excluded from the analysis to correct for the poor fit (Cal/EPA, 1992). A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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National Cancer Institute (NCI) 1978. Bioassay of Cupferron for Possible Carcinogenicity. CAS No. 135-20-6. Carcinogenesis Technical Report Series No. 100. NCI-CG-TR-140. DHEW Publication No. (NIH) 78-1350. U.S. Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

2, 4-DIAMINOANISOLE

CAS No: 615-05-4

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	138.17
Boiling point	not available
Melting point	67-68 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 5.651 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 6.6 E-6 ($\mu g/m^3$)$^{-1}$
Slope Factor: 2.3 E-2 (mg/kg-day)$^{-1}$
[Male rat thyroid tumors (NCI, 1978), contained in Gold *et al*. (1984) database, expedited Proposition 65 methodology (Cal/EPA, 1992), with cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of 2,4-diaminoanisole in humans are known to exist.

Animal Studies

Male and female Fischer 344 (F344) rats and B6C3F$_1$ mice were fed diets containing 2,4-diaminoanisole (DAA) sulfate (NCI, 1978). Mice were fed diets containing 1200 or 2400 mg/kg DAA sulfate for 78 weeks and were observed for an additional 18-19 weeks. Rats were fed diets containing 5000 mg/kg DAA sulfate for 78 weeks, or diet containing 1250 mg/kg DAA sulfate for 10 weeks, then 1200 mg/kg diet for 68 weeks, followed by a 29 week observation period. Matched control groups were provided for each dose group. Group sizes were 50 animals/sex/species/group with the exception of the male rat high-dose control group (49 animals). Mortality of control and treated rats and mice were similar by the end of the study. Significantly increased incidences of thyroid tumors were seen in both mice (males - follicular cell adenomas; females - follicular cell adenomas, carcinomas) and rats (follicular cell adenocarcinomas, carcinomas, papillary adenocarcinomas and cystadenocarcinomas). Increased skin tumor incidences (squamous-cell carcinomas, basal-cell carcinomas, sebaceous adenocarcinomas) were observed in male rats. Male and female rats both had increased incidences of preputial or clitoral gland adenomas, papillomas or carcinomas and Zymbal gland tumors (males - squamous cell carcinomas, sebaceous adenocarcinomas; females - sebaceous adenocarcinomas). Tumor incidence data is listed in Table 1.

Table 1 Tumor induction in Fischer 344 rats and B6C3F$_1$ mice by dietary administration of 2,4-diaminoanisole (NCI, 1978)

Sex/species	Dose group	Average Dose[1] (mg/kg-day)	Tumor type	Tumor Incidence[2]
Male mouse	control	0	thyroid	1/100
	low dose	116		0/50
	high dose	234		11/50
Female mice	control	0	thyroid	0/100
	low dose	126		0/50
	high dose	253		8/50
Male rats	control	0	thyroid	2/99
	low dose	35.2		2/50
	high dose	146		17/50
	control	0	preputial gland	0/99
	low dose	35.2		2/50
	high dose	146		8/50
	control	0	skin	0/99
	low dose	35.2		2/50
	high dose	146		9/50
	control	0	Zymbal gland	0/99
	low dose	35.2		1/50
	high dose	146		6/50
Female rats	control	0	thyroid	3/100
	low dose	44		1/50
	high dose	182		10/50
	control	0	clitoral gland	3/100
	low dose	44		5/50
	high dose	182		8/50
	control	0	Zymbal gland	0/100
	low dose	44		0/50
	high dose	182		4/50

1. Doses reported by Gold *et al*., 1984.
2. Tumor incidences reported by Gold *et al*., 1984.

Diets containing 2,4-diaminoanisole at concentrations of 0, 1200, 2400 or 5000 mg/kg diet were fed to female F344 rats (40 - 60/group) for up to 82-86 weeks (Evarts and Brown, 1980). An additional 15 rats were fed diet containing 5000 mg/kg diet for 10 weeks, then fed control diet and observed for up to 87 weeks. Thyroid tumor incidences (follicular-cell adenomas or carcinomas or C cell carcinomas) were 1/37 in controls, 2/47 in the low-dose group, 3/33 in the mid-dose group and 31/40 in the high-dose group; in addition, 3/12 animals exposed to the 5000 mg/kg diet for 10 weeks had thyroid tumors. Clitoral gland tumors (squamous-cell, sebaceous-cell or squamous-sebaceous-cell carcinomas) were noted in 0/37 controls, 8/47 of the low-dose

group, 15/33 of the mid-dose group and 9/40 of the high dose-group, as well as in 1/12 of the animals in the 10 week high-dose group.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Cancer potency for 2, 4-diaminoanisole was derived from that for the sulfate using a molecular weight conversion (Cal/EPA, 1992):

$$q_h\,(\text{base}) = q_h\,(\text{sulfate}) \times \frac{\text{MW(sulfate)}}{\text{MW(base)}}$$

where q_h is the human potency and MW is the molecular weight. This conversion assumes that the intake of equivalent moles of the two forms of the chemical results in equivalent concentrations of the active species *in vivo*. Gold et al. (1984) list the results of the NCI (1978) feeding studies in male and female F344 rats and $B6C3F_1$ mice, and the feeding study by Evarts and Brown (1980) in female F344 rats. Cancer potency is based on dose-response data for benign and malignant thyroid tumors in male rats, the most sensitive sex and species (see Table 1) (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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2, 4-DIAMINOTOLUENE

CAS No: 95-80-7

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	122.17
Boiling point	292 °C
Melting point	99 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 4.997 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.1 E-3 $(\mu g/m^3)^{-1}$
Slope Factor: 4.0 E+0 $(mg/kg\text{-}day)^{-1}$
[Female rat mammary gland tumors (NCI, 1978), contained in Gold *et* al. database (1984), expedited Proposition 65 methodology (Cal/EPA, 1992), cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the carcinogenic potential of 2,4-diaminotoluene in humans are known to exist.

Animal Studies

IARC (1978) reviewed a study by Umeda (1955) in which 20 rats of mixed strain and sex were injected subcutaneously with 0.5 ml of a 0.4% solution of 2,4-diaminotoluene at weekly intervals. No tumor induction was noted in 11 rats that died in the first 8 months of the study. All 9 surviving rats, which received 29-44 weekly injections, developed subcutaneous sarcomas. No concurrent control group was included in this study; however, another group of 12 rats exposed to 11 subcutaneous injections of xanthene in propylene glycol over 10 months did not develop local sarcomas.

Male Wistar rats were fed diets containing 0, 0.06% or 0.1% 2,4-diaminotoluene for 30-36 weeks (12 animals/treatment group, 6 animals/control group) (Ito *et al.*, 1969). Exposure to 2,4-diaminotoluene caused an increased incidence of hepatocellular carcinomas in the treated animals (0/6, 7/11, and 9/9 in the control, low-dose and high-dose groups, respectively).

Male and female Fischer 344 (F344) and B6C3F_1 mice were fed diets containing 2,4-diaminotoluene (NCI, 1979). Treatment group sizes were 50 animals/sex/species/group; matched control group sizes were 20 animals/sex/species/group. The study design is outlined in Table 1. Male and female rat low- and high-dose levels were reduced after 40 weeks.

Table 1. Experimental design of 2,4-diaminotoluene carcinogenicity bioassay using male and female F344 rats and B6C3F$_1$ mice (NCI, 1979)

Sex/species	Study group	dietary 2,4-diaminotoluene (ppm)	Study time (weeks)	Time-weighted average dose[c] (ppm)
Male rat	matched control	0	103	0
	low dose	125	40	
		50	63	79
	high dose	250	40	
		100	39[a]	176
Female rat	matched control	0	103	0
	low dose	125	40	
		50	63	79
	high dose	250	40	
		100	44[b]	171
Male,female mouse	matched control	0	101	
	low dose	100	101	
	high dose	200	101	

a. Test diet administration was terminated at the time indicated and all high-dose males were killed because of morbidity.

b. Test diet administration was terminated at the time indicated and all high-dose females except four were killed because of morbidity.

c. Time-weighted average dose $= \dfrac{\sum (\text{dose in ppm} \times \text{weeks at that dose})}{\sum (\text{weeks recieving each dose})}$

Significantly increased tumor incidences were observed in treated rats; hepatocellular adenomas, carcinomas and neoplastic nodules in male and female rats, mammary gland adenomas and carcinomas in female rats, and subcutaneous fibromas in male rats. Significant increases in tumor incidence were also noted in female mice; hepatocellular carcinomas in the low- and high-dose groups, and lymphomas in the low-dose group. No significant tumor induction was noted in male mice. Tumor incidence data is listed in Table 2.

Table 2. 2,4-Diaminotoluene-induced tumor incidence in F344 rats and B6C3F$_1$ mice (NCI, 1978)

Sex/species	Study group	Average dose[a] (mg/kg-day)	Tumor type	Tumor incidence[b]
Male rats	matched controls	0	liver tumors[c]	0/20
			subcutaneous fibromas	0/20
	low dose	3.2	liver tumors[c]	5/50
			subcutaneous fibromas	15/50
	high dose	7.0	liver tumors[c]	10/50
			subcutaneous fibromas	19/50
Female rats	matched controls	0	liver tumors[c]	0/20
			mammary gland tumors	0/20
	low dose	3.95	liver tumors[c]	0/50
			mammary gland tumors	11/50
	high dose	8.55	liver tumors[c]	6/50
			mammary gland tumors	14/50
Female mice	matched controls	0	liver tumors	0/20
			lymphomas	2/20
	low dose	13.0	liver tumors	13/50
			lymphomas	29/50
	high dose	26.0	liver tumors	18/50
			lymphomas	11/50

a. Doses as reported by Gold *et al*. (1984).
b. Tumor incidences as reported by Gold *et al*. (1984)
c. Includes hepatocellular neoplastic nodules, adenomas and carcinomas

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Results of the NCI (1978) feeding studies of 2, 4-diaminotoluene in male and female B6C3F$_1$ mice and F344 rats are listed by Gold et al. (1984). Significant increases in tumors were seen in rats of both sexes and in female mice. The study results indicated that rats are more sensitive than mice. The female rat appears to be slightly more sensitive than the male, although the study is not sensitive enough to definitively distinguish between the two. Cancer potency is based on mammary gland tumors in the female rat (see Table 2).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. Because female rat survival was poor in this study, the potency was derived using a time-to-tumor analysis (Crump et al., 1991; Cal/EPA, 1992). The individual

animal data for the time-to-tumor analysis were obtained from TOX_RISK (Crump et al., 1991). A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

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1,2-DIBROMO-3-CHLOROPROPANE

CAS No: 96-12-8

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1995)

Molecular weight	236.36
Boiling point	195.5°C
Melting point	5°C
Vapor pressure	0.8 mm Hg @ 21°C
Air concentration conversion	1 ppm = 9.67 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.9 E-3 $(\mu g/m^3)^{-1}$
Slope Factor: 7.0 E+0 $(mg/kg\text{-}day)^{-1}$
[Calculated from a cancer potency factor derived by RCHAS/OEHHA (CDHS, 1988)]

III. CARCINOGENIC EFFECTS

Human Studies

Two occupational epidemiological studies, Hearn *et al*. (1984) and Wong *et al*. (1984), were conducted using data from workers exposed during the formulation or manufacture of 1,2-dibromo-3-chloropropane (DBCP). The study by Hearn *et al*. (1984) examined a cohort of 550 chemical workers exposed to a variety of compounds, including DBCP. Twelve of the subjects in this cohort died from cancer (7.7 expected). In the study by Wong *et al*. (1984) 9 cases of respiratory cancer were reported in a cohort of 1034 workers exposed to DBCP (5.0 expected). Neither of these studies produced statistically significant ($p < 0.05$) associations between DBCP exposure and expected cancer incidence. In addition, it was not possible to account for all confounding chemical exposures in these studies. Therefore these studies were considered by IARC (1987) to be inadequate and were not used for the derivation of the cancer potency of DBCP.

An epidemiological study conducted by Jackson *et al.* (1982) found an association between DBCP in drinking water and increased incidence of stomach cancer and leukemia. In this study, patterns of DBCP contamination of well water in Fresno County, California were compared with deaths from selected cancers in the same area from 1970 to 1979. The cancers studied included stomach, esophageal, liver, kidney, and breast cancers in addition to lymphoid leukemia. Significant relationships between DBCP exposure level and cancer deaths were tested by Bartholomew's trend test. Exposed individuals were grouped into those with less than 0.05 ppb, those with 0.05 up to 1.0 ppb, and those with greater than 1.0 ppb DBCP in the drinking water. Mortality was age-adjusted using 20-year age groups. Significant trends for incidence of stomach cancer and lymphoid leukemia were found. Results may have been confounded by smoking habits, ethnicity, and exposure to other carcinogens.

Additional analysis of these data by Environmental Health Associates (EHA, 1986) and sponsored by the Shell Oil Company did not show the above association. These data included corrections for ethnicity. This study used a different method for estimating DBCP concentrations. Although the associations between cancer incidence and DBCP exposure failed to reach significance at the $p < 0.05$ level in the EHA study, the magnitude of the associations in the high and low exposure groups were approximately the same as described in the Jackson et al. (1982) study. The trend for cancer risk and DBCP exposure is most closely related to the time of residence of the test subjects (Table 1).

Table 1. Relative risk of human gastric cancer in areas with high[1] concentrations of dbcp in the drinking water compared with areas of low[2] DBCP (Jackson *et al*., 1982).

Time of Residence	Relative Risk for Gastric Cancer
1 year at death	1.29
1 year prior to death	1.55
10 years prior to death	3.05

[1] DBCP concentrations greater than 1.0 ppb.
[2] DBCP concentrations less than 0.05 ppb.

Animal Studies

DBCP is a carcinogen in at least two laboratory rodent species by inhalation, ingestion, or dermal exposure. Tumors following DBCP exposure can arise not only at the site of application, but also at distal sites. Because of its carcinogenicity to multiple species, DBCP is assumed to represent a carcinogenic threat to humans (CDHS, 1985).

Three sets of long-term bioassays using mice and rats were conducted respectively by the National Cancer Institute (NCI, 1978), the National Toxicology Program (NTP, 1982) and Hazelton Laboratories (1977, 1978). In the NCI (1978) study, DBCP was administered by oral gavage to both sexes of rats and mice. Two major problems with this study, early mortality and nearly 100% forestomach carcinoma rate, precluded its usefulness in determining a cancer potency value. The inhalation study by NTP (1982) had much better survival rates than those observed in the gavage study, and carcinogenicity was observed for tissues at or near the site of the initial chemical contact.

In the NTP study, groups of 50 B6C3F1 mice or 50 F344 rats of either sex were exposed by inhalation to 0, 0.6 or 3.0 ppm DBCP for 6 hours/day, 5 days/week, for 76-103 weeks. Surviving high-dose rats were killed at week 84. High-dose female mice and low- and high-dose male mice were killed at week 76. Low-dose rats and female mice were killed at week 104. A significant increase in the combined incidence of nasal tumors was found in male and female rats at both concentrations (Table 2a, 2b). In mice, the combined incidence of nasal tumors was significantly increased in females at both concentrations, and in males exposed to the high concentration.

Proliferative lesions were observed at sites distal to the lung in the mice, including the kidney, forestomach, and spleen.

Table 2a. Incidence of combined nasal cancers from DBCP Inhalation exposure in rats and mice (NTP, 1982)

	Tumor Incidence DBCP Concentration (ppm)		
Species	0	0.6	3.0
F-344 Rats (males)	0/50	32/50	39/49
F-344 Rats (females)	1/50	21/50	32/50
B6C3F1 Mice (males)	0/45	1/42	21/48
B6C3F1 Mice (females)	0/50	11/50	38/50

Table 2b. Incidence of combined lung cancers from DBCP inhalation exposure in mice (NTP, 1982)

	Tumor Incidence DBCP Concentration (ppm)		
Species	0	0.6	3.0
B6C3F1 Mice (males)	0/41	3/40	11/45
B6C3F1 Mice (females)	4/50	12/50	18/50

In the studies conducted by the Hazelton Laboratories (1977, 1978), mice (50 males or females per group) or rats (60 males or females per group) were exposed to DBCP in the diet for 78 weeks. The intended daily doses were 0, 0.3, 1.0 and 3.0 mg/kg per day. Both species exhibited dose-dependent increases in forestomach squamous cell papillomas and carcinomas. The mouse study contained experimental errors in the diet preparation and food consumption measurements. Spillage of the food and evaporation in the mouse study may have resulted in an overestimate of the actual average daily exposure. For the rats, diets were prepared every two weeks, therefore loss of DBCP in the food due to evaporation was less significant than in the mouse study. The average amount of DBCP in the diet was estimated assuming first-order evaporation loss (Shell Oil Company, 1986). Using this model, the average daily doses of DBCP in the mouse study were 0, 0.3, 1.6 and 4.8 mg/kg per day. The study conducted by Hazelton Laboratories used lower doses than those in the NCI study, providing better information on the lower end of the dose-response curve. However, the times of death or times of tumor appearance were not reported. In addition, the study conducted by Hazelton Laboratories was terminated at 78 weeks in the case of the mice but lasted for 104 weeks in the case of the rats.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The Hazelton Laboratories (1977) study in female CD-1 mice was chosen as the critical study for the derivation of the cancer potency factor. In this study, female mice had a tumor incidence of 19/50 in the high dose group. No tumors were observed in the controls, and no histopathological examination was determined in the low and mid dose groups. The problem of food spillage and evaporation of the DBCP from the food bias the data toward an underestimation of the true cancer potency. Despite this fact, the data from this study gives a higher potency than that calculated from the rat data. The cancer potency for DBCP is based on the incidence of forestomach squamous cell carcinomas in the Hazelton Laboratory study, and is consistent with the incidence of stomach carcinomas in female mice in the NCI gavage study. In addition, the inhalation study conducted by NTP produced tumors at sites distal to the lung, including the forestomach. The cancer potency based on the NTP inhalation study is close to, but slightly lower than the potency derived from the Hazelton Laboratories study. The Hazelton Laboratory study was therefore taken to be the most appropriate animal data for the derivation of the cancer potency value.

Based on the calculated cancer potency derived from the animal studies, significant increases in cancer incidence would not be expected in the human occupational studies. The duration of exposure was too brief, the exposure too recent, and the number of subjects too small. In the ecological and case-control environmental studies by Jackson *et al*. (1982) and EHA (1986), a significant increase in the number of cancers would indicate that the true human cancer potency is an order of magnitude higher than that calculated from the animal studies.

Methodology

A linearized multistage model was used to estimate the cancer potency of DBCP from the Hazelton Laboratories (1977) data in female CD-1 mice (Crump et al., 1982). The actual daily doses received by the mice were estimated to be 0, 0.3, 1.6 and 4.8 mg/kg/day (Shell Oil Company, 1986). The 95% upper confidence bound on the dose-response slope was used to derive the human cancer potency value for DBCP.

The animal cancer potency, q_{animal}, was calculated from the linear slope using the lifetime scaling factor $q_{animal} = q_1^* \times (T/T_e)^3$, where T/T_e is the ratio of the experimental duration to the lifetime of the animal. An estimated value for the human cancer potency was determined using the relationship $q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$, where bw is the default body weight of human or animal (mouse).

Using these relationships, a human cancer potency (q_{human}) of 6.6 $(mg/kg \times day)^{-1}$ was derived (CDHS, 1988). An airborne unit risk factor was calculated by OEHHA/ATES from the q_{human} value using the default parameters of 70 kg human body weight and 20 m^3/day breathing rate.

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1,4 - DICHLOROBENZENE

CAS No: 106-46-7

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1995)

Molecular weight	147.01
Boiling point	174°C
Melting point	53.1°C
Vapor pressure	10 mm Hg @ 25°C
Air concentration conversion	1 ppm = 6 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.1 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 4.0 E-2 $(mg/kg\text{-}day)^{-1}$
[Calculated from a cancer potency factor derived by CDHS (1988)]

III. CARCINOGENIC EFFECTS

Human Studies

There are several case reports of human leukemia associated with occupational exposure to chlorinated benzenes, including 1,4 - dichlorobenzene (1,4-DCB) (Girard *et al*., 1969). One case of chronic lymphocytic leukemia involved exposure to a solvent mixture of 80% ortho-, 2% meta-, and 15% para-dichlorobenzene. The association between leukemia and 1,4 - dichlorobenzene exposure was confounded by multiple chemical exposure.

Animal Studies

Loeser and Litchfield (1983) conducted a chronic inhalation carcinogenicity bioassay in male and female Alderly Park rats. In this study, groups of 76-79 rats were exposed to 0, 75, or 500 ppm p-DCB 5 hours/day, 5 days/week for 76 weeks. Control rats exhibited a high mortality rate and did not differ significantly from treated rats in overall tumor incidence (Table 1) or in the incidence of animals with multiple tumors and malignant tumors.

Table 1. Tumor incidence in rats exposed to 1,4-dichlorobenzene (DCB) in air for 76 weeks (Loeser and Litchfield, 1983)

Concentration of 1,4-DCB	Combined Tumors (males)	Combined Tumors (females)
0 ppm	39/60	55/61
75 ppm	31/60	54/61
500 ppm	35/60	53/58

A parallel experiment was conducted using groups of 75 Swiss mice of either sex (Loeser and Litchfield, 1983). In this experiment, female mice were exposed to 0, 75, or 500 ppm 1,4 - DCB for 5 hours/day, 5 days/week, for 57 weeks. A similar experiment in male mice was terminated due to high mortality due to fighting and respiratory infections. As with the rats, no significant increase in any tumor type was detected.

The National Toxicology Program (NTP, 1987) studied the carcinogenicity of 1,4 - DCB in male and female F344 rats and B6C3F1 mice via chronic (103 week) oral intubation. Male rats were given 0, 150, or 300 mg/kg 1,4 - DCB for 5 days/week for 103 weeks. Male and female mice, and female rats were given 0, 300, or 600 mg/kg for the same duration. Sentinel animals were killed periodically to test for infectious pathogenic agents. The survival of male rats given 300 mg/kg was significantly lower than controls after 97 weeks, but the survival of treated female rats was unchanged from controls. The time-weighted average doses in the study were 0, 214, and 428 mg/kg/day for the mice, and 0, 107, and 214 mg/kg/day for the rats. Male rats treated with 1,4-DCB displayed nephropathy and mineralization and hyperplasia of renal tubules. The incidence of renal tubular adenocarcinomas was also dose-dependently increased in the male rats (1/50, 3/50, or 7/50 for the 0, 107, or 214 mg/kg groups, respectively). A significant dose-dependent increase in the incidence of mononuclear cell leukemia (5/50, 7/50, or 11/50 for the 0, 107, or 214 mg/kg groups, respectively) was observed in the male rats. Additionally, an increasing trend in the incidence of mesothelioma was observed in the male rats (1/50, 0/50, 4/50, for the 0, 107, or 214 mg/kg groups, respectively).

Mice of both sexes exposed to 1,4 - DCB had significantly increased incidence of hepatocellular adenomas and carcinomas (NTP, 1987). In addition, four male mice exposed to 428 mg/kg were found to have hepatoblastomas, a rare hepatocellular carcinoma. The incidence of follicular thyroid cell adenomas was increased in female mice exposed to 428 mg/kg ($p < 0.038$). As with the male rats, male mice showed evidence of kidney tubule damage when treated with 1,4 - DCB. Females were not similarly affected.

NTP concluded from these data that 1,4 - DCB was carcinogenic to male rats, but not female rats. In addition, NTP concluded that the increased incidence of hepatocellular adenomas and carcinomas was evidence of carcinogenicity in male and female mice.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The study by NTP (1987) was chosen by CDHS (1988) as the key study for the development of a cancer potency value for 1,4-DCB. In the NTP (1987) study, mice and rats exhibited significant increases in several types of tumors. The mice were exposed for 5 days/week, resulting in average daily doses of 0, 214, and 428 mg/kg/day 1,4-DCB. Mice of either sex exhibited a significant increase in hepatocellular carcinomas or adenomas. The incidence of hepatocarcinomas or adenomas was 17/50, 22/49, and 40/50 in the control, 214, and 428 mg/kg/day groups, respectively. In addition, male rats showed a significant increase in kidney

adenomas and mononuclear cell leukemia. The cancer potency for 1,4-DCB was calculated from the male mouse hepatocarcinoma and adenoma data.

Methodology

A linearized multistage model was used to estimate the cancer potency of 1,4-DCB from the NTP (1987) data in male B6C3F1 mice (Crump *et al*., 1982). The concentrations of 1,4-DCB given in the feed were 0, 214, or 428 mg/kg/day. The premature mortality of animals without tumors was subtracted from the sample groups. The 95% upper confidence bound on the dose-response slope was used to derive the human cancer potency value.

The animal cancer potency, q_{animal}, was calculated from the linear slope using the lifetime scaling factor $q_{animal} = q_1^* \times (T/T_e)^3$, where T/T_e is the ratio of the experimental duration to the lifetime of the animal. In this case, the scaling factor was equal to 1. An estimated value for the human cancer potency was determined using the relationship $q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$, where bw is the default body weight of human or animal (mouse).

Using these relationships, a human cancer potency (q_{human}) of 0.04 $[mg/kg \times day]^{-1}$ was calculated (CDHS, 1988). An airborne unit risk factor of 1.1E-5 $(\mu g/m^3)^{-1}$ was calculated by OEHHA/ATES from the q_{human} value using the default parameters of 70 kg human body weight and 20 m^3/day breathing rate.

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3,3-DICHLOROBENZIDINE

CAS No: 91-94-1

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	253.1
Boiling point	402°C
Melting point	132-133°C
Vapor pressure	unknown
Air concentration conversion	1 ppm = 10.4 mg/m^3 (IARC, 1982)

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 3.4 E-4 $(\mu g/m^3)^{-1}$
Slope Factor: 1.2 E+0 $(mg/kg\text{-}day)^{-1}$
[Calculated from a cancer potency factor derived by RCHAS/OEHHA (CDHS, 1988)]

III. CARCINOGENIC EFFECTS

Human Studies

The body of literature addressing the carcinogenicity of 3,3'-dichlorobenzidine in humans is scant. Three retrospective epidemiological studies of occupational exposure have been conducted, focusing on the possibility that 3,3'-dichlorobenzidine is a bladder carcinogen like its parent compound, benzidine. None of the studies approximates exposure levels.

Gerarde and Gerarde (1974) conducted a study of 175 workers involved in the manufacture and use of dichlorobenzidine in a chemical manufacturing plant in the United States between 1938 and 1957. Workers were segregated from benzidine exposure. No bladder tumors were found among the exposed workers. General population incidence of bladder tumors predicts 0-2 cases in a cohort of this size.

Gadian (1975) conducted a study of 35 British workers exposed to dichlorobenzidine who had been segregated from exposure to benzidine in a chemical plant from 1953 to 1973. Cumulative hours of exposure were tabulated for all workers. No tumors were reported among the exposed workers at the end of the study (through 1973).

MacIntyre (1975) reports on bladder tumor incidence among 225 Scottish production and service workers, 119 of which had more than 5 years of exposure to dichlorobenzidine and 36 of which were exposed more than 16 years before the time of the study. No bladder tumors were reported among the study subjects.

Animal Studies

Stula *et al.* (1975) conducted a study on ChR-CD rats (50/sex/group), exposing animals to 1000 ppm 3,3'-dichlorobenzidine in feed for life (mean survival 51 weeks), with an interim exposed group of 6 rats/group sacrificed after 12 months. Control animals receiving no added compound were observed for up to two years (mean survival 81 weeks (males) and 90 weeks (females)). Male animals showed statistically significant increases in incidences of granulocytic leukemias (9/44 treated vs. 2/44 control; $p<0.05$ by Fisher's exact test), mammary adenocarcinomas (7/44 treated vs. 0/44 control; $p<0.01$), and Zymbal gland carcinomas (8/44 treated vs. 0/44 control; $p<0.01$). Female animals only showed increased incidence of mammary adenocarcinomas (26/44 treated vs. 3/44 control; $p<0.01$).

Stula *et al.* (1978) later conducted a study on six female beagle dogs, administering 100 mg 3,3'-dichlorobenzidine in gelatin capsules 3 times/week for 6 weeks followed by 100 mg, 5 times/week for up to 7.1 years, plus 6 untreated control animals sacrificed at 8-9 years of age. One animal which died during the course of the study (3.5 years) showed no sign of tumors, whereas another animal which died at 6.6 years showed both undifferentiated liver carcinoma and papillary transitional cell carcinoma of the bladder. Among the animals surviving to the end of the study there was an increased incidence of hepatocellular carcinoma (3/4 treated vs. 0/6 control; $p<0.05$) and papillary transitional cell carcinoma of the bladder (4/4 treated vs. 0/6 control; $p<0.01$). Control animals showed a high incidence of adenocarcinoma and carcinoma of the mammary gland (4/6).

Pliss (1959) reports on carcinogenesis in Rappolovskii white rats exposed to 3,3'-dichlorobenzidine in feed for 12 months. The addition of 10-20 mg added to feed in the form of a paste (50% with water) 6 days/week resulted in an estimated total dose of 4.5 g/animal. A group of 130 animals receiving injections of octadecylamine and methylstearylamine were termed a "historical control". Twenty-two of 29 animals were examined for tumors at the time of the first tumor's appearance. Findings included tumors of Zymbal gland (7/29), mammary gland (7/29), skin (3/29), bladder (3/29), hematopoietic system (3/29), adenocarcinoma of the ileum (2/29), connective tissue (2/29), salivary gland (2/29), liver (1/29), and thyroid (1/29). No tumors were reported among "control" animals. Pliss (1959, 1963) also conducted studies exposing rats to 3,3'-dichlorobenzidine by the subcutaneous route. In the first study (Pliss, 1959), animals (25 female, 36 male) received 120 mg 3,3'-dichlorobenzidine weekly for 10-11 months. The dose was reduced to 20 mg/rat after the sixth month due to toxicity. The same "control"animals were used as with the feeding study. The author notes the appearance of tumors of the Zymbal gland (10/35), mammary gland (6/35), skin (5/35), hematopoietic system (2/35), connective tissue (2/35), salivary gland (1/35), and local subcutaneous sarcomas (7/35) among animals surviving to the time of the appearance of the first tumors.

Griswold *et al.* (1968) dosed 20 female Sprague-Dawley rats with 300 mg 3,3'-dichlorobenzidine in sesame oil by gavage (10 doses at three day intervals) and observed the animals after 9 months for incidence of mammary tumors. Control groups included a negative control (sesame oil only) and a positive control (7,12-dimethylbenz[a]anthracene). No tumors were observed in treated

animals, but a 3% incidence was observed in the negative controls and 100% incidence in positive control animals.

Osanai *et al.* (1976) treated 26 male ICR/JCL mice (plus 39 untreated control mice) with feed containing 0.1% 3,3'-dichlorobenzidine for 12 months with an interim sacrifice group at 6 months. Hepatomas were observed in all treated animals at 6 and 12 months ($p<0.01$) and among control animals at an incidence of 0%, 9.5% (2/21) and 38.55% (5/13) at 6,12, and 18 months, respectively.

Tatematse *et al.* (1977) fed 22 male Wistar rats a diet containing 0.3% 3,3'-dichlorobenzidine alone or in sequence with o-N-butyl-N-(4-hydroxybutyl)nitrosamine (0.1% in drinking water), N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (0.15% in the diet) and N-fluorenylacetamide (0.025% in the drinking water) over a four week period. Twelve untreated animals served as controls. Animals were observed for a 40 week period. Only animals receiving combined exposures showed effects which included some bladder tumors and histological changes of the liver.

Saffiotti *et al.* (1967) and Sellakumar *et al.* (1969) report on a feeding study in which Syrian golden hamsters (30/sex/group) were exposed to 0.1% or 0.3% 3,3'-dichlorobenzidine in feed; an untreated control group (30/sex) was included. No significant carcinogenic effects were observed in the 0.1% 3,3'-dichlorobenzidine group. The 0.3% 3,3'-dichlorobenzidine group, however, showed increased incidence of transitional cell carcinomas of the bladder (4/30 treated, 0/30 control; $p=0.056$ by Fisher's exact test). Other observations included some liver-cell and cholangiomatous tumors.

A single study suggests that 3,3'-dichlorobenzidine may act as a transplacental carcinogen (Golub *et al.*, 1974). Pregnant female BALB/c mice given 2 mg 3,3'-dichlorobenzidine (in 0.1 ml sesame oil) five times during the last week of pregnancy, showed increased incidence of lymphoid leukemia among the offspring of exposed animals (7/24 treated, 0/30 control; $p<0.01$). This effect, however, could also have occurred by exposure via lactation.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

An IARC (1982) review of the human epidemiological studies deemed them inadequate for evaluating carcinogencity due to the relatively small size of the cohorts, inadequate time since first exposure, and/or incomplete follow-up of exposed workers.

The only carcinogenesis studies amenable to the development of cancer potency values are those conducted by Stula *et al.* (1975, 1978) showing the induction of granulocytic leukemia, mammary adenocarcinoma, and Zymbal gland carcinoma in rats and papillary transitional cell carcinomas of the bladder and hepatocellular carcinomas in beagle dogs exposed to 3,3'-dichlorobenzidine. Limitations of the other available studies including poor study design,

inadequate scope of endpoints, and unclear interpretation of dose extrapolation, preclude the development of cancer potency values from these studies.

Methodology

The most sensitive experimentally determined endpoint for tumor development is mammary adenocarcinoma induction in female rats exposed to 3,3'-dichlorobenzidine (26/44 treated, 3/44 control) (Stula *et al*., 1975). A linearized multistage model (CDHS, 1985) applied to these data resulted in an estimation of the upper 95% confidence bound of cancer potency (q_1^*) of 0.023 $(mg/kg\text{-}day)^{-1}$. With a study duration of 49.9 weeks for females (T_e) and a natural lifespan assumption of 104 weeks (T), the cancer potency for animals (q_{animal}) was derived to be 0.21 $(mg/kg\text{-}day)^{-1}$ from the following relationship:

$$q_{animal} = q_1^* \times (T/T_e)^3$$

Human cancer potency (q_{human}) of 1.2 $(mg/kg\text{-}day)^{-1}$ based upon body weight assumptions of 0.35 kg for female rats (bw_a) and 70 kg for humans (bw_h) and the following relationship:

$$q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$$

A unit risk value of 3.4 E-4 $(\mu g/m^3)^{-1}$ based upon air concentrations was derived by OEHHA/ATES assuming a human breathing rate of 20 m^3/day, a human body weight of 70 kg, and 100% fractional absorption after inhalation exposure.

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1, 1-DICHLOROETHANE

CAS No: 75-34-3

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	98.97
Boiling point	57.3°C (ATSDR, 1990)
Melting point	-96.7°C (ATSDR, 1990)
Vapor pressure	230 mmHg at 25°C (ATSDR, 1990)
Air concentration conversion	1 ppm = 4.05 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.6 E-6 $(\mu g/m^3)^{-1}$
Slope Factor: 5.7 E-3 $(mg/kg\text{-}day)^{-1}$
[Female rat mammary gland adenocarcinoma tumor data (NCI, 1977), contained in Gold *et* al. database (1990), expedited Proposition 65 methodology (Cal/EPA, 1992), cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of 1,1-dichloroethane in humans are known to exist.

Animal Studies

Male and female Osborne-Mendel rats and $B6C3F_1$ mice were exposed to 1,1-dichloroethane dissolved in corn oil by gavage (NCI, 1977). The study design is summarized in Tables 1a and 1b. Dosing was performed once/day, 5 days/week. Dosing of the low- and high-dose mouse treatment groups was performed cyclically in the latter part of the experimental period; one exposure-free week was followed by 4 weeks of exposure.

Dose-related increases were noted in mammary adenocarcinomas and hemangiosarcomas in female rats. Statistically significant increases were observed in endometrial stromal polyps in high-dose female mice (4/46 compared to 0/79 for controls, $p = 0.017$) and in hepatocellular carcinomas in high-dose male mice (8/32 compared to 6/72 in pooled vehicle controls, $p = 0.027$). Female rat tumor incidence data is listed in Table 2.

Klaunig *et al*. (1986) exposed male $B6C3F_1$ mice to 1,1-dichloroethane in drinking water for 52 weeks. Exposure levels were 0, 835 and 2500 mg/l. Group sizes were 35 mice/group; 10 mice/group were killed after 24 weeks. Histology was only performed on kidney, liver and lung

samples. No treatment-related increase in tumor incidence was noted. However, histological examination was only performed on a limited number of tissues, and only male mice were used.

Table 1a. Study design for carcinogenicity bioassay of 1,1-dichloroethane (1,1-DCE): Osborne-Mendel rats (NCI, 1977)

Sex	Group	Group Size	1,1-DCE dose (mg/kg bw)	Observation period (weeks)		Time-weighted average dosage[1] (78 weeks)
				Treated	Untreated	
Male	Untreated control	20	0		109	0
	Vehicle control	20	0	78	33	0
	Low dose	50	350	8		382
			450	23		
			450[2]	37	10	
			0		33	
	High dose	50	700	8		764
			900	23		
			900[2]	37	10	
			0		33	
Female	Untreated control	20	0		105	0
	Vehicle control	20	0	78	33	0
	Low dose	50	750	8		475
			900	9		
			450	14		
			450[2]	37	10	
			0		33	
	High dose	50	1500	8		950
			1800	9		
			900	14		
			900[2]	37	10	
			0		33	

1. Time weighted average dosage = $\sum$ [(dosage $\times$ number of weeks) / 78 weeks]
2. Gavage doses were cyclically administered; one exposure-free week was followed by 4 weeks (5 days/week) of exposure at the exposure level indicated.

Table 1b. Study design for carcinogenicity bioassay of 1,1-dichloroethane (1,1-DCE): $B6C3F_1$ mice (NCI, 1977)

Sex	Group	Group Size	1,1-DCE dose (mg/kg bw)	Observation period (weeks)		Time-weighted average dosage[1] (78 weeks)
				Treated	Untreated	
Male	Untreated control	20	0		90	0
	Vehicle control	20	0	78	12	0
	Low dose	50	900	6		1442
			1200	3		
			1500	69		
			0		13	
	High dose	50	1800	6		2885
			2400	3		
			3000	69		
			0		13	
Female	Untreated control	20	0		91	0
	Vehicle control	20	0	78	12	0
	Low dose	50	900	6		1665
			1200	3		
			1500	11		
			1800	58		
			0		13	
	High dose	50	1800	6		3331
			2400	3		
			3000	11		
			3600	58		
			0		13	

1. Time weighted average dosage = $\sum$ [(dosage $\times$ number of weeks) / 78 weeks]

Table 2 Tumor induction in female Osborne-Mendel rats after gavage exposure to 1,2-dichloroethane (NCI, 1977)

Dose group	Average dose[1] (mg/kg-day)	Tumor type	Tumor incidence[2]
vehicle control	0	mammary adenocarcinomas hemangiosarcomas	0/20 0/40
low dose	238	mammary adenocarcinomas hemangiosarcomas	1/50 0/50
high dose	477	mammary adenocarcinomas hemangiosarcomas	5/50 4/50

1. Dose as reported by Gold *et al*., 1984. 2. Tumor incidence as reported by Gold *et al*., 1984

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Gold *et al*. (1984) list the results of the NCI (1977) gavage studies in male and female B6C3F$_1$ mice and Osborne Mendel rats. Cancer potency for 1, 1-dichloroethane is based on mammary gland adenocarcinomas observed in female rats, the most sensitive of the species/sex combinations tested (see Table 2). Because female rat survival was poor in this study, the potency was derived using a time-to-tumor analysis (Crump et al., 1991; Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

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DI-(2-ETHYLHEXYL)PHTHALATE

CAS No: 117-81-7

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	390.54
Boiling point	230°C @ 5 mm Hg
Melting point	-50°C
Vapor pressure	1.32 mm Hg @ 200°C
Air concentration conversion	1 ppm = 16.0 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.4 E-6 $(\mu g/m^3)^{-1}$
Slope Factor: 8.4 E-3 $(mg/kg\text{-}day)^{-1}$
[calculated from a cancer potency value derived for a Proposed Maximum Contaminant Level (CDHS, 1988)]

III. CARCINOGENIC EFFECTS

Human Studies

Thiess *et al.* (1978; reviewed by US EPA, 1994) report on a study of mortality among 221 workers involved in di-(2-ethylhexyl)phthalate (DEHP) production. Potential exposure periods range from 3 months to 24 years and the mean follow-up period was 11.5 years. Among workers exposed for more than 15 years, incidences of pancreatic carcinoma (1 case) and uremia (1 case with urethral and bladder papillomas) were elevated over incidence in the corresponding age group of the general population. No quantitation of exposure levels was reported.

Animal Studies

The National Toxicology Program (NTP, 1982; Kluwe *et al.*,1982) assayed the carcinogenic effects of di-(2-ethylhexyl)phthalate on rats and mice. Fischer F344 rats (50/sex/group) were treated with diet containing 0, 6000, or 12000 ppm DEHP for 103 weeks. $B6C3F_1$ mice (50/sex/group) were treated with diet containing 0, 3000, or 6000 ppm DEHP for 103 weeks. Survivors were sacrificed and examined histologically at 105 weeks. Survival of rats was not found to be significantly influenced by DEHP treatment. Increased incidence of hepatocellular carcinoma or hepatic neoplastic nodules was reported in male and female high-dose treated rats (see Table 1). The increase in incidence was found to be dose-related ($p<0.01$). Among treated high-dose male and female mice, and low-dose female mice, hepatocellular carcinoma incidence was increased. The increase in incidence was found to be dose-related ($p<0.05$).

Table 1. Incidence of hepatocellular carcinoma in male and female $B6C3F_1$ mice and F344 rats fed diet containing DEHP (NTP, 1982).

species	treatment[1] (ppm in diet)	hepatocellular carcinoma incidence	
		male	female
F344 rats	0	3/50	0/50
	6,000	6/49	2/49
	12,000	12/49[2]	8/50[3]
$B6C3F_1$ mice	0	9/50	0/50
	3,000	14/48	7/50[3]
	6,000	19/50[2]	17/50[4]

[1] Fischer F344 rats were treated with 0, 6000, or 12000 ppm DEHP in their diet for 103 weeks. $B6C3F_1$ mice were treated with 0, 3000, or 6000 ppm DEHP in their diet for 103 weeks. Survivors were sacrificed after 105 weeks.
[2] $p<0.05$. [3] $p<0.01$. [4] $p<0.001$.

Carpenter *et al.* (1953) maintained 2 month old Sherman rats (32/sex/group) on a diet containing 0, 400, 1300, or 4000 ppm DEHP up to two years. Animals were sacrificed at one year with the exception of a subgroup of a maximum of 8 rats/sex/dose which were exposed for an additional year. A group of 80 F_1 generation rats, the progeny of females in the highest dose group exposed for more than 120 days, were exposed for one year to diet containing 4000 ppm DEHP. Survivors were sacrificed after one year. No malignant tumors were observed among treated animals. Three rats in the 4000 ppm DEHP dose group, four in the 1300 dose group, two in the 400 ppm dose group, and five in the control group were reported to have benign tumors. Two benign tumors in the treated F_1 rats (vs. one in the control group) had benign tumors. Mortality at two years was reported to be 70.3% among control animals and between 60 and 70% among the treated groups. Poor survival of animals precluded evaluation of carcinogenicity from this study.

Carpenter *et al.* (1953) also treated hybrid guinea pigs (~23/sex/dose) with diet containing 0, 1300, or 4000 ppm DEHP for 1 year, at which time animals were sacrificed. Survival among exposed animals was decreased. No carcinogenic effects were observed.

Carpenter *et al.* (1953) also treated 4 dogs with gelatin capsules containing a volume of 0.03 ml/kg body weight DEHP five days per week for 19 doses, then with 0.06 ml/kg body weight DEHP for 240 doses. Four control animals were also included in the study. No tumors were observed in treated or control animals.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The only data appropriate for the development of a cancer potency value come from the NTP (1982) study which showed a dose-related effect of DEHP on the incidence of hepatocellular carcinoma in Fischer 344 rats and $B6C3F_1$ mice. This study was conducted by standard protocols with an adequate number of animals and thorough reporting of results.

Methodology

For the purpose of developing a cancer potency in humans, US EPA (1986, 1987) converted the exposure levels of rats and mice in the NTP (1982) study to human equivalent doses (HEDs). Dosage levels were first converted from parts per million in the diet to mg/kg-day based upon reported food disappearance rates. The resulting daily low and high dose estimates were 322 and 674 mg/kg-day for male rats, 394 and 774 mg/kg-day for female rats, 672 and 1325 mg/kg-day for male mice, and 799 and 1821 mg/kg-day for female mice. HEDs were based on the following relationship, with D the applied dose level, bw_a the experimental animal body weight, bw_h the assumed human body weight, l_e the length of exposure, L_e the length of the study, and L the lifespan of the animal:

$$HED = D \times \frac{l_e}{L_e} \times \left(\frac{bw_a}{bw_h}\right)^{\frac{1}{3}} \times \left(\frac{L_e}{L}\right)^3$$

Using the derived HED values, US EPA (1987) applied the multistage model of Howe and Crump (Global 82; 1982) to the combined incidence data of hepatocellular carcinomas and neoplastic nodules reported by NTP (1982). The resulting upper 95% confidence bounds on the cancer potency (q_{human}) are presented in Table 2. The highest, and thus most sensitive, cancer potency value is derived from the incidence of hepatocellular carcinomas in male $B6C3F_1$ mice, with a q_{human} value of 8.4 E-3 $(mg/kg\text{-}day)^{-1}$. Selection of the cancer potency value for DEHP comes from the most sensitive site and species of tumor induction in experimental animals in the absence of human data appropriate for developing a potency value.

Table 2. Human cancer potency values derived by US EPA (1986, 1987) from the NTP (1982) study.

species	sex	q_{human} $[(mg/kg\text{-}day)^{-1}]$
F344 rats	male	2.95 E-3
	female	3.52 E-3
$B6C3F_1$ mice	male	8.36 E-3
	female	4.73 E-3

A unit risk value of 2.4 E-6 $(\mu g/m^3)^{-1}$ was derived by OEHHA/ATES assuming a 70 kg average human body weight, 20 m^3/day human breathing rate, and 100% fractional absorption.

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p-DIMETHYLAMINOAZOBENZENE

CAS No: 60-11-7

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	225.28
Boiling point	not available
Melting point	114-117 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 9.214 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.3 E-3 ($\mu g/m^3$)$^{-1}$
Slope Factor: 4.6 E+0 (mg/kg-day)$^{-1}$
[Female rat liver tumor data (Kirby and Peacock, 1947), contained in Gold *et al.* database (1984), expedited Proposition 65 methodology (Cal/EPA, 1992), cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of *p*-dimethylaminoazobenzene (DAB) in humans are known to exist.

Animal Studies

IARC (1974) reviewed a number of studies on the carcinogenic potential of DAB in animals. DAB was initially reported by Kinosita (1937) to induce liver tumors in rats after dietary exposure; tumors were produced after 50 or more days of treatment (smallest total dose, 176 mg DAB). Sherman, Wistar and Evans rats were found to be equally susceptible to the induction of liver tumors after exposure to diets containing 600 mg/kg DAB (Sugiura and Rhoads, 1941).

Kirby and Peacock (1947) exposed male and female Wistar-derived rats to a low-protein diet (12% casein) containing 0 or 600 mg/kg diet DAB. Group sizes were 8 animals/sex/group except for treated females, where the group consisted of 7 animals. Four male rats received treated diet for 28 weeks, followed by control diet; the other animals received treated diet for 33 weeks. At the end of the treatment period, all animals received control diet until sacrifice at 52 weeks. Both male and female rats developed hepatomas; Gold *et al*. (1984) list a tumor incidence of 0/8 and 5/7 for control and treated (average dose, 20.9 mg/kg-day) females, respectively.

Druckrey and Küpfmüller (1948; reviewed by IARC, 1975) exposed rats to 1, 3, 10, 20 or 30 mg DAB/day by gavage for the life of the animals. All doses induced the formation of liver tumors; the induction time was inversely proportional to the dose, ranging from 34 days (30 mg/day) to 700 days (1 mg/day). For exposure groups in the 3-30 mg/day range, the total carcinogenic dose was about 1000 mg. Daily exposures of 0.1 or 0.3 mg/rat did not induce tumors.

Druckrey (1967) exposed rats to 5 mg DAB/rat by gavage for 40, 60, 100, 140 or 200 days, then observed the animals for the remainder of their lifespan. Percent incidences of liver carcinomas were 20, 26, 49, 80 and 81, respectively.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The feeding study by Kirby and Peacock (1947) conducted in Wistar-derived albino rats is listed in Gold *et al*. (1984). Cancer potency is based on liver tumors in the female rats.

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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